POST-ISCHEMIC REACTIVE HYPEREMIA IN THE DIAGNOSIS OF PERIPHERAL ARTERIAL OBSTRUCTIVE DISEASE.

Peter Frans Verhagen

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To my parents.

CHAPTER I

INTRODUCTION

I.1 Introduction

In the last two decades major advances have been made in the development and application of different non-invasive methods for use in the diagnosis of arterial obstructive disease of the lower extremities. The main objectives of these new methods have been to provide a functional assessment of the vascular system. Clinicians and vascular surgeons need simple, reliable and reproducible investigatory tests, not only for screening purposes, but also for the follow-up of patients to assess the results of treatment. Blood pressure measurements at different levels of the leg at rest, and during reactive hyperemia are tests that have been widely accepted and are used in most vascular laboratories. The application of tests such as blood pressure measurements at different levels of the leg, have provided not only an objective assessment of the severity of the disease, but have also encouraged a more judicious use of angiography. With technological advances, tests with more and more sophistication have been introduced. Only some of them realized their expectations as simple, reliable and accurate and others lost credibility when they were used inappropriately eg. systolic ankle blood pressures to localize the level of arterial disease. Uncertainty still exists as to the accuracy and practical value of the various methods used in the functional assessment of arterial insufficiency of the lower extremities (1). This study was undertaken to clarify the indications for certain diagnostic methods in the functional analysis of arterial insufficiency and to provide guidelines as to their use.

I.2 Aim of the study

The aim of this study was therefore to answer the following questions:
- Which method identifies patients with functionally significant, arterial insufficiency of the lower extremities?
- Which method best quantifies the degree of arterial obstructive disease?
- Is it possible to detect multiple level disease and localize the hemodynamically most significant lesions, and predict the outcome of a vascular reconstruction?
- Which methods are the most practical, applicable and reliable in clinical practice?

I.3 Contents of the thesis

This thesis is divided in two parts. The first part is a literature review. Chapter II contains aspects about the hemodynamics and (patho-)physiology of the arterial circulation. Chapters III and IV contain a review of the various tests used in the diagnosis of arterial obstructive disease. Chapter V contains a comparison of postexercise and postischemic ankle blood pressures. The postischemic reactive hyperemia test (PIRH) was found simple to perform and was used for the following studies. In chapters V, VI and VII, the PIRH test with measurement of the systolic blood pressure at the ankle is described. Chapters VI and VII contain a reproducibility study of the PIRH test and the value of the PIRH test with ankle pressure measurements in vascular diagnosis is assessed. Chapter VII also contains a discussion about the value of ankle pressures during PIRH compared to the value of ankle pressures measured only at rest in a group of patients with symptoms of arterial obstructive disease. As expected from the experience of others, the localization of hemodynamically, significant lesions in the arterial tree could not be assessed by ankle blood pressure measurement alone. Direct femoral systolic blood pressure measurements at rest and during PIRH were used to assess the aorto-iliac segment in multilevel disease. Chapter VIII contains a retrospective and chapter IX contains a prospective study, using direct femoral artery pressure measurements during PIRH in groups of patients with angiographically, demonstrated multilevel disease, to asses the aorto-iliac segment. Chapter X, summarizes the conclusions and contains recommendations based on the findings of this study.

1. Sumner D.S.
Presidential address: non-invasive testing of vascular disease - Fact, fancy, and future.
Surgery 1983; 93: 664-669

CHAPTER II

THE HEMODYNAMICS AND (PATHO-)PHYSIOLOGY OF THE ARTERIAL CIRCULATION.

- With the exception of some purely anatomic lesions, such as aneurysms, the pathophysiology of peripheral circulatory disease is largely a study in energy depletion -

- David S. Sumner -

II.1 Introduction

This chapter is not a complete review of the hemodynamics and (patho-)physiology of the arterial circulation. Excellent textbooks and articles are available for a more thorough review of the subject (1-7). In this chapter some basic principles are highlighted as they aid the understanding and the interpretation of the vascular diagnostic tests, examined in this study.

II.2 Basic principles

II.2.1 Fluid energy (1-3)

Total fluid energy (E) consists of potential- and kinetic energy. Potential energy consists of a component due to internal pressure and a component due to gravitational forces. The intravascular, internal pressure is produced by cardiac contraction and the elastic properties of the vascular wall. Gravitational potential energy in the vascular system represents the ability of a volume of blood to do work because of its elevation above a given point.
Kinetic energy in the vascular system represents the ability of blood to do work because of its velocity. Assuming blood to be an incompressible fluid it can be deduced from the momentum equation that in a stationary state without heat conduction and viscous losses, the total fluid energy per unit volume of blood can be written as:

$$E/VOL = P + \rho gh + 0.5\rho v2 \qquad Nm2$$

In this equation P is the internal pressure. ρgh is the gravitational potential energy per unit volume of blood and $0.5\rho v2$ is the kinetic energy per unit volume of blood. ρ is the specific gravity of blood, g the gravitation constant, h the distance above a given reference level and v the blood flow velocity.

II.2.2 Loss of energy associated with blood flow (1-3)

As blood flows through the arterial tree, it loses energy due to frictional forces. The total fluid energy per unit volume of blood thus changes from one point (1) to another (2). The basic Bernouilli equation for rigid tubes which assumes that the total fluid energy per unit of volume is constant from one point to another cannot be applied. The basic Bernouilli equation is given by the formula:

$$P1 + \rho gh1 + 0.5\rho v2/1 = P2 + \rho gh2 + 0.5\rho v2/2$$

In the arterial tree, heat conduction and viscous losses occur. Moreover the vascular wall is not rigid but (visco-)elastic, which means that total fluid energy can be converted into potential, elastic energy of the vascular wall or can be lost because of the viscous properties of the vascular wall. Thus the basic Bernouilli equation has to be rewritten:

$$P1 + \rho gh1 + 0.5\rho v2/1 = P2 + \rho gh2 + 0.5\rho v2/2 + \text{losses}$$

Viscous losses in the blood are determined by the coefficient of viscosity of blood. The coefficient of viscosity is defined as the friction between contiguous layers of blood.
Poiseuille's law defines the drop in potential energy per unit volume in steady (non-pulsatile), laminar flow in a straight cylindrical tube with rigid walls assuming a parabolic flow profile within the tube. The drop in internal pressure between two points in the tube is given by:

$$P1 - P2 = Q \cdot 8\eta l/\pi r4$$

l is the distance between the points. Q is the flow in the tube. r is the inside radius of the tube and η is the coefficient of viscosity. In vivo the conditions of Poiseuille's law are never completely fullfilled. This means that the energy loss is always higher than that predicted by Poiseuille's law. These concepts are illustrated in figure 1.
Figure 1 emphasizes that application of Poiseuille's law greatly underestimates the pressure drop across an arterial segment. The inertial energy losses at the entrance (contraction) and the exit (expansion) of the stenosis are greater than the viscous energy losses given by Poiseuille's law (8-11).
Sudden changes in flow velocity, due to changes in vessel diameter, the pulsatility of the applied pressure and the turbulence in flow, cause a drop in internal pressure. This pressure drop is converted in heat due to inertia of the blood mass and is proportional to the square of the flow velocity:

$$P = k\ 0.5\ \rho v2$$

All these factors compound the energy losses of blood in the circulation. The energy loss between any two points within the arterial tree may be several times that predicted by Poiseuille's law (12.13). Poiseuille's law cannot thus be used alone to predict pressure -flow relationships in the arterial tree. It can only be used to define the minimum energy losses expected under any given flow state (9).

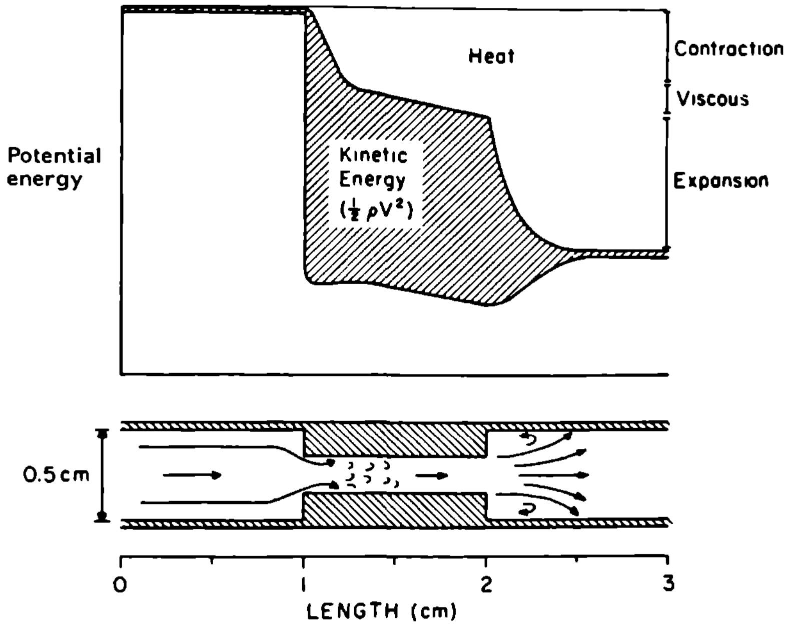

Figure 1. Diagram illustrating energy losses experienced by blood passing through a stenosis 1 cm. long. Flow is assumed to be unidirectional and steady. Note that very little of the total energy loss is attributable to "viscous" losses. Thus, applications of Poiseuille's law greatly underestimate the pressure drop across an arterial stenosis.

Redrawn from Rutherford R.B.: "Vascular Surgery", W.B. Saunders, Philadelphia, London, Toronto, 1977, figure 4-6.

II.3 Hemodynamic resistance and impedance

Hemodynamic resistance or hemodynamic impedance, refering to steady and pulsatile flow conditions respectively (6), has been defined as the ratio of the energy fall per unit of volume between two points along a blood vessel, to the blood flow in the vessel (3).
Unlike electrical resistance, hemodynamic resistance is non lineair

and does not remain constant over a wide range of flows (3).
Total limb impedance is composed of segmental (iliac-, femoral- and crural arteries or collaterals bypassing these vessels) resistances and run-off resistances (arterioles, capillaries and venules) (14-16). Collaterals, representing the segmental resistance when main arterial channels are occluded, are considered by some authors to be fixed resistances, (3) whereas others have found small falls of these resistances during hyperemia (14.16.17). Although the mechanism of collateral enlargement is the subject of much debate, it appears to be related to an increased pressure gradient across preexisting pathways (18-20), and to an increased blood flow velocity through these pathways (18.20.21). The increase in segmental resistance in patients with arterial obstructions, is greatly compensated for by a reduction of the run-off resistance (14.16). Therefore the drop in total peripheral resistance caused by exercise or ischemia is less in lower extremities with arterial obstructive disease than in normal limbs (40-70% as compared to 90% in healthy legs) (14).

II.4 Pressure-flow relationships across arterial stenoses.

Viscous energy losses are increased by narrowed segments through which the blood must pass. Flow disturbances, contraction and expansion phenomena increase inertial energy losses. These energy losses are manifested by a decrease in pressure and flow.
Since the body tends to maintain flow at normal levels by dilatation of the peripheral vessels to compensate for an increased resistance to arterial supply, an increased pressure gradient is the first objective sign of an arterial stenosis (1).
Only when the peripheral resistance vessels have reached a state of maximal vasodilatation will further decrease in the lumen of the stenotic vessel result in impaired flow (1).

II.4.1 Critical stenosis

The concept of critical stenosis has long been popular with vascular surgeons (8-10, 22-25). It is usually defined as the percentage by which the cross-sectional area of a vessel must be reduced in order to produce a measurable drop in blood flow and pressure.
Figure 2 illustrates the concept of critical stenosis.
Beyond a certain percentage of area reduction, blood flow and blood pressure decrease precipitously. There is one other point that must be made and that is shown in figure 2. Pressure drops are critically dependent upon blood flow velocity, so that to say that a certain value is "the critical stenosis" is meaningless unless the flow rate is specified (26-28).
In figure 2 this is shown by the fact that in high peripheral resistance, low flow states the curve is shifted to the right. In high flow states (as during hyperemia) a stenosis will be critical with less cross-sectional area reduction than in low flow states.
It should be noted that figure 2 represents an experimental situation in which collateral and run-off resistance were considered to be fixed.

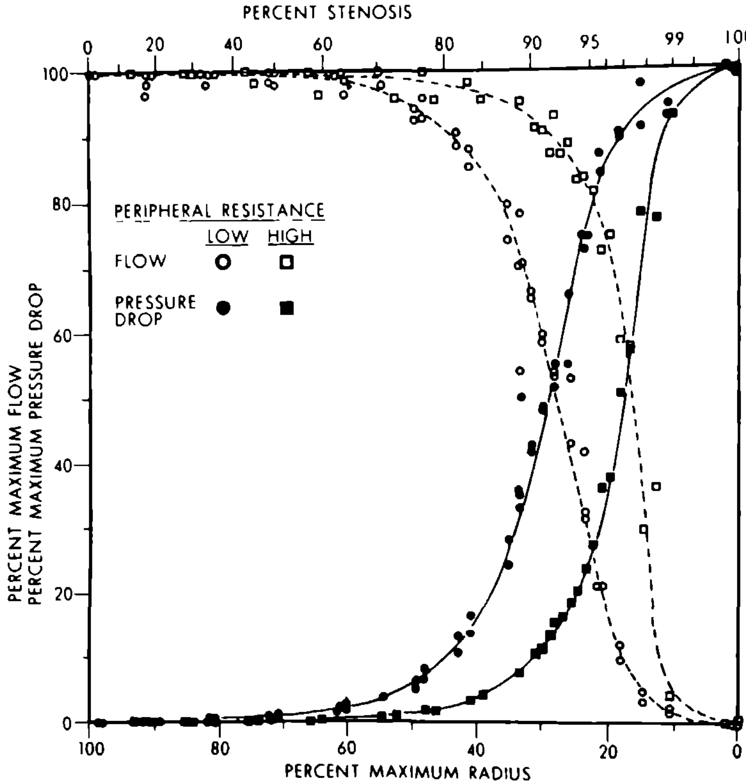

Figure 2. Relationship of pressure and flow to degree of stenosis in a canine femoral artery. When peripheral resistance is high, the curves are shifted to the right. Note that percentage change in flow through the stenosis is essentially a mirror image of the percentage of maximal pressure drop across the stenosis.

Redrawn from Rutherford R.B.: "Vascular Surgery", W.B. Saunders, Philadelphia, London, Toronto, 1977, figure 4-7.

In the (patho-)physiologic situation, arterial stenoses do no exist in isolation but are part of a complex hemodynamic circuit (1.25) (fig. 3).

In the case of a slowly developing arterial stenosis, typical of human atherosclerotic disease, the resistance of the run-off bed (Rp) and possibly the collateral resistance (Rc) tend to decline, resulting in a constant total resistance of the entire vascular circuit (Rt). This insures that the total resting flow (Qt), will remain unchanged.

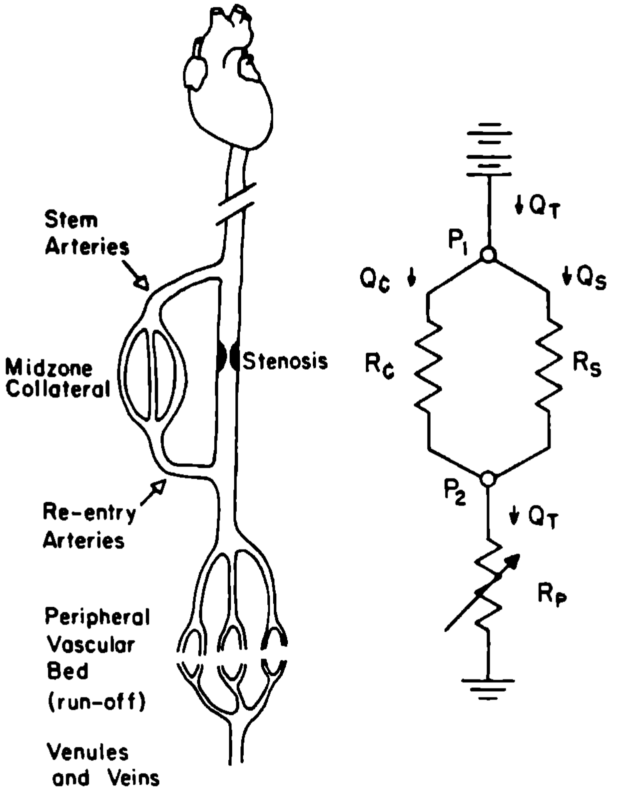

Figure 3. Diagram illustrating the major components of an arterial circuit containing a stenotic major artery. Right-hand panel shows an electric analogue of this circuit. The battery at the top represents the potential energy source, i.e., the heart; ground potential, at the bottom, indicates the central veins. Other symbols are: Q_T, total flow; C_C, collateral flow; and Q_S, flow through the stenotic artery. Resistances are: R_C, collateral; R_S, stenotic artery; and R_P, peripheral "run-off" bed. R_C and R_S are relatively "fixed"; R_P is "variable".

Redrawn from Rutherford R.B.: "Vascular Surgery", W.B. Saunders, Philadelphia, London, Toronto, 1977, figure 4-8.

Surprisingly enough these events have little influence on the concept of critical stenosis. If one assumes that the collateral resistance (Rc) remains unchanged, the resistance of the vascular segment will increase as the arterial stenosis increases. If the flow (Qt) through the entire circuit is kept constant by lowering the run-off resistance (Rp), then the pressure drop (P1-P2) across the stenosis will be greater than if no compensatory resistance changes had occurred. Consequently, because of the increased pressure drop, the flow through

the stenosis (Qs) will be slightly higher for any given degree of stenosis than that which would have been present had there been no drop in the run-off resistance.
If, in addition to the resistance changes in the run-off bed, the collateral resistance (Rc) also falls, the pressure drop between points P1 and P2 will be less for a given stenosis than it would have been without the compensatory resistance changes. However, the flow through the stenosis will be somewhat less since more of the flow is diverted through the low resistance collaterals. Thus, within physiologic ranges for resting flow to the lower extremities, compensatory resistance changes in the collateral channels and the run-off bed do not appreciably alter the shape of the critical stenosis curve as given in figure 2 (1). Thus the concept of critical stenosis can be used clinically, when combined with knowledge of the blood flow velocity which mainly depends on peripheral resistances.

II.5 Conclusion

Precise attemps to relate pressure and flow restriction to percentage stenosis are frustrated by the irregular geometry of the vascular lesions and by the nonlinearity of pulsatile blood flow. The most instructive formulae are those which incorporate the viscous and inertial effects on blood flow and blood pressure (8-11.25.26.29.30). The concept of critical stenosis is useful when conditions of flow are defined (1). Under resting conditions a stenosis causing greater than 80% cross-sectional area reduction is usually significant (26). When flow rates are increased a much lower degree of narrowing may constitute a critical stenosis (1). For this reason, diagnostic blood pressure studies should preferably be performed during high flow states such as during hyperemia.

1. Strandness D.E., Sumner D.S.
Hemodynamics for surgeons
Grune and Stratton, New York, 1975

2. Mc Donald D.A.
Blood flow in arteries
Williams & Wilkens Co., Baltimore 1974

3. Rutherford R.B.
Vascular Surgery, Ed. Rutherford
W.B. Saunders Co., Philadelphia, 1977

4. Bruyninckx C.M.A.
Pre- en postoperatieve evaluatie van claudicatio intermittens met behulp van een Doppler flowmeter
Thesis, Nijmegen, 1976

5. Buth J.
Het vasculair laboratorium
Thesis, Amsterdam, 1978

6. Kitslaar P.J.E.H.M.
Doppler ultrasound tests in the diagnosis of chronic aorto-iliac obstruction
Thesis, Maastricht, 1982

7. Boer J. de
Stroming in slagaderen
Bohn, Scheltema en Holkema, Utrecht, 1978

8. May A.G., DeWeese J.A., Rob C.G.
Hemodynamic effects of arterial stenosis
Surgery 1963a; 53: 513

9. Byar D., Fiddian R.V., Querean M., et al.
The fallacy of applying the Poiseuille equation to segmental arterial stenosis
Am. Heart J. 1965; 70: 216

10. Berguer R., Hwang N.H.C.
Critical Arterial Stenosis: a theorical and experimental solution
Ann. Surg. 1974; 180: 39

11. Young D.F., Tsai F.Y.
Flow characteristics in models of arterial stenoses -II unsteady flow-
J. Biomechanics 1973; 6: 547

12. Ling S.C., Atabek H.B., Letzing W.G., Patel D.J.
Non-linear analysis of aortic flow in living dogs
Circ. Res., 1973; 33: 198

13. Milnor W.R.

Pulsatile blood flow
N. Engl. J. Med., 1972; 287: 27

14. Ludbrook J.
Collateral artery resistance in human lower limb
J. Surg. Res. 1966; 6: 423-434

15. Strandness D.E.
Peripheral arterial disease. A physiological approach
Churchill, London, 1969

16. Sumner D.S.
The hemodynamics and pathophysiology of arterial disease
In: Vascular surgery (Ed. Rutherford R.B.).
Saunders, Philadelphia, 1977; chapter 4: pp 25-46

17. Bernink P.J.L.M.
Parameters van de circulatie in de onderste extremiteiten met betrekking tot atherosclerosis obliterans
Thesis, Groningen, 1978

18. Conrad M.C., Anderson J.L., Garret J.B.
Chronic collateral growth after femoral artery occlusion in the dog
J. Appl. Physiol., 1971; 31: 550

19. John H.T., Warren R.
The stimulus to collateral circulation
Surgery 1961; 49: 14

20. Rosenthal S.L., Guyton A.C.
Hemodynamics of collateral vasodilation following femoral artery occlusion in anesthetized dogs
Circ. Res. 1968; 23: 239

21. Winblad J.N., Reemtsma K., Vernhet J.L., et al.
Etiologic mechanisms in the development of collateral circulation
Surgery 1959; 45: 105

22. Fiddian R.V., Byar D., Edwards E.A.
Factors affecting flow through a stenosed vessel
Arch. Surg. 1964; 88: 105

23. Mann F.C., Herrick J.F., Essex H.E., Baldes E.J.
The effect on the blood flow of decreasing the lumen of a blood vessel
Surgery 1938; 4: 249

24. Brice J.G., Dowsett D.J., Lowe R.D.
Hemodynamic effects of carotid artery stenoses.
Br. Med. J. 1964; 2: 1363

25. Roth A.C., Young D.F., Cholvin N.R.
Effect of collateral and peripheral resistance on blood flow through

arterial stenosis
J. Biomechanics 1976; 9: 367

26. May A.G., van de Berg L., DeWeese J.A., Rob C.G.
Critical arterial stenosis
Surgery 1963b; 54: 250

27. Sydorak G.R., Moore W.S., Newcomb L., et al.
Effects of increasing flow rates and arterial caliber on critical arterial stenoses
Surgical Forum 1972; 23: 243

28. van de Berg L., DeWeese J.A., Rob C.G.
The effect of arterial stenosis and sympathectomy on blood flow and the ergogram
Ann. Surg. 1964; 159: 623

29. Young D.F., Cholvin N.R., Kirkeeide R.L., Roth A.C.
Hemodynamics of arterial stenoses at elevated flow rates
Circulation Research 1977; 41: 99

30. Young D.F., Cholvin N.R., Roth A.C.
Pressure drop across artificially induced stenoses in the femoral arteries of dogs
Circulation Research 1975; 36: 735

CHAPTER III

DIAGNOSIS OF ARTERIAL OBSTRUCTIVE DISEASE OF THE LOWER EXTREMITIES

III.1 History and physical examination

History and physical examination are of prime importance in making a correct diagnosis. Patients usually present with key complaints which often give a diagnosis even before examination is carried out.
One of the most important complaints is pain, either at rest or during exercise (intermittent claudication). The anamnestic walking distance and the claudication distance are of relative importance (1). Hylkema (2) concluded from his study that there was no correlation between the anamnestic walking distance and the treadmill relative claudication time. He also found no correlation between treadmill claudication time and systolic ankle pressure at rest, and after exercise. Other authors, however, have found a correlation between anamnestic exercise tolerance and systolic ankle pressures (chapter VII). Anamnestic claudication time is dependent on more factors than the arterial insufficiency alone (chapter IV.2.2) and history taking therefore is of prime importance in deciding upon the influence of these other factors. Rest pain is a symptom of severe obstructive disease and nearly always will multiple level disease be present (3.4). There is no direct relation between the level of occlusive disease and the localization of pain (3.4).
Physical examination has been described in textbooks (5). The most important signs in the diagnosis of arterial obstructive disease are to be found in the character of arterial pulsations and in the presence and character of bruits. The interpretation of arterial pulsations is very subjective. Pulsations can be weak without arterial obstructive disease (6) and can be present and apparently normal in the presence of obstructive disease (7.8). In the latter case, the pulsations will most often disappear or become weaker during hyperemia (7). A correct assessment of femoral pulsations is rather difficult (1). Brener et al (9) reported a strong femoral pulse in 23% of cases with a hemodynamically important iliac stenosis, and in 33% a weak pulse in the absence of significant disease. Auscultating for bruits over arteries at rest and during hyperemia is an important aspect in physical examination, although there are some controversies over the interpretation of findings. Gupta and Wiggers (10) could not find a correlation between intensity of a bruit and degree of stenosis. Wylie and McGuinness (11) found the loudest bruit occured in the presence of asymptomatic iliac stenoses. Finally, it is important to realize that aneurysms can also cause bruits (12).

III.2 Angiography

Angiography of the lower extremities can be performed by the translumbar, transfemoral and transaxillary routes. Translumbar angiography is performed by direct puncture of the aorta, transfemoral and transaxillary angiography by means of the Seldinger technique. Angiography is an invasive procedure and has its own morbidity and mortality rates. These, however are not high. Terpstra (12) reported 0.1% serious complications due to translumbar angiography. Szilagyi et al (13) reported 0.5% serious complications with his technique. Lang (14) described a mortality of 0.06% and 0.7% serious complications in a serie of 11.402 transfemoral angiographies. In other studies serious complications have been reported to occur in up to 14% (5). An aorto-iliac angiogram provides limited hemodynamic information and even the sensitivity and specificity of biplanar angiography in this regard is unsatisfactory (9). Numerous reports have shown that angiograms can be misleading in predicting hemodynamics (ref. 1-3.5.7-19 chapter IX). Finally, it has been shown that an angiogram is unreliable in the assessment of collaterals (15.16) and in the prediction of the outcome of a femoro-popliteal bypass, based on the angiographic appearance of the crural vessel (17.18). Angiography is valuable for planning the strategy of an operation, but the decision for surgical treatment should be based on other investigations as angiography provides mainly anatomical and little physiological information.

III.3 Blood pressure measurements

The measurement of systolic blood pressure can be performed both directly and indirectly. A good correlation exists between the indirect (cuff) pressure values and the direct (intra-arterial) measurements (19.20).

III.3.1 Indirect blood pressure measurement by means of a cuff

This technique is simple, the equipment relatively inexpensive and the method more sensitive than blood flow measurements (21-24). Basically one needs a pneumatic cuff and a flow detector, such as a Doppler ultrasonic velocity detector (24), a plethysmograph or other suitable device (5). The usual level of measurement is at the ankle, just superior to the malleoli. In this position the standard arm cuff (12 cm width) is suitable (1). Blood pressures measured at the level of the thigh or calf (segmental blood pressure measurements) should not be performed with the standard cuff. This cuff is too narrow for these levels and relatively high blood pressures will be obtained. A cuff with a width of approximately 1.2 times the diameter of the part around which it is placed, should be used (1). The level at which the pressure is determined, is given by the position of the cuff and not by that of the Doppler probe (1.2.).

Ankle blood pressures at rest and during hyperemia

Of all non-invasive tests available for use in diagnosing arterial insufficiency, none is more useful than the measurement of the systolic blood pressure at the ankle (5.24). The method is simple, inexpensive, reproducible and is based on sound physiological principles. The reproducibility of the ankle-arm pressure index at rest is also excellent and a variance of 0.05-0.15% has been reported in different studies (25). The diagnostic value of ankle pressures at rest and during PIRH is extensively discussed in chapter VII. The response of ankle blood pressure during hyperemia in healthy persons and in patients with arterial obstructive disease is discussed in chapter IV. Excellent reviews on the subject can also be found in the theses of Bruyninckx (1), Kitslaar (26), Hylkema (2) and in textbooks (5.27).

Segmental blood pressures at rest and during hyperemia

Segmental pressure measurements are indicated when the ankle pressure is abnormal, to determine the site of the stenosis or obstruction. The segmental pressures may be expressed as longitudinal gradients along the leg, as a gradient between the arm and the leg pressures, or as a leg over arm pressure index (5.26). Either blood pressure gradients or indices can be used for diagnostic purposes (1.28). Normal and pathologic values for segmental pressures at different levels can be found in the theses of Bruyninckx (1) and Kitslaar (26) and in textbooks (5.27). Thigh pressures are not only dependent on the hemodynamic state of the aorto-iliac segment, but also upon the width of the cuff, the level of the cuff on the thigh and the hemodynamic states of the superficial and the deep femoral arteries (1.26.29-32). Even the proposal that a normal thigh pressure index excluded significant aorto-iliac obstruction (32), was disproved by Fronek et al (33). Kitslaar (26) calculated accuracies, specificities and sensitivities for the test, from the data of several authors (1.2.29.30), who used thigh pressures to diagnose aorto-iliac disease. Specificities were as low as 46% (30). Bruyninckx (1) reported relatively good values. He used a rather complicated method which compared ankle-arm and thigh-arm pressure differences. He reported an accuracy of 94%, specificity of 97% and sensitivity of 82%. The best results (accuracy 96%, sensitivity 95%, specificity 96%) were reported by Heintz et al (29), using a combination of high and low thigh pressure measurements. All the above mentioned studies used angiography as the gold standard. Flanigan et al (34) used direct intra-arterial pressure measurements of the femoral artery as their gold standard, in evaluating the high-thigh segmental pressure method. They found the method only 79% sensitive, 56% specific and 63% accurate in the prediction of hemodynamically significant aorto-iliac disease. Faris and Jamieson (30), and Bernink (35) reported that measurements of the thigh pressure during hyperemia did not increase the diagnostic value of the test, in assessing the aorto-iliac segment. Masafumi Hirai and Schoop (36), however, stated that thigh pressures at rest have no diagnostic value, but that post-exercise thigh pressure measurements are of considerable value in assessing the aorto-iliac segment (table 1). They included more patients with isolated aorto-iliac disease than with multiple level disease and it is especially in those with multiple level disease that the value of thigh pressure measurements is controversial.

III.3.2 Direct intra-arterial blood pressure measurements
Direct intra-arterial blood pressure measurement in the common femoral artery is the most commonly used invasive technique for assessing the aorto-iliac segment. Measurements are frequently performed during angiography through the catheters or needles already positioned for the contrast injections (ref 14.15.17, chapter IX). Intravascular pressures measured through catheters or needles are subject to error due to the effect of kinetic energy ($\frac{1}{2}\rho v2$). If the catheter is aligned to the oncoming blood end-on, the pressure recorded will be too high by a factor of $\frac{1}{2}EV2$. On the other hand, if the catheter faces downstream, the recorded pressure will be too low by the same factor. In a normal aorta, these errors are approximately 1.0 mm Hg and are therefore inconsequential (5). The instrumentation necessary for measuring arterial blood pressure by invasive techniques consist of a manometer and a hydraulic system for the transmission of intravascular pressure. It can safely be stated that tight stop-cock connections and avoidance of air trapping and air bubbles in the hydraulic system are of prime importance. The catheters should be made of stiff materials (polyethylene or teflon) and catheter length should be kept to a minimum. The use of the newer solid-state pressure transducers with a very high frequency response and little or no fluid volume will greatly improve overall system characteristics (27). It is useful to combine direct femoral artery pressure studies with hyperemia, and PIRH can be easily combined with this method (chapter IX). The method is also of value in the presence of distal arterial obstructive disease (9) and many authors believe that this method gives superior results (3.9.34). Chapters VIII and IX deal extensively with direct arterial pressure measurements during PIRH and contain a review of the literature and our own experience. Table 1 summarizes the results of this method in assessing the aorto-iliac segment, as they were found in the recent literature.

III.4 Blood flow measurements

Flow in a blood vessel can be measured directly but invasively by an electromagnetic flow meter. More frequently used in the diagnosis of arterial insufficiency of the lower extremities are venous occlusion plethysmography and isotope clearance techniques. Venous occlusion plethysmography is non-invasive and isotope clearance studies require only the injection of an isotope. Buth (28) and Bruyninckx (1) have given extensive descriptions of both techniques. The two techniques are almost exclusively performed at the level of the calf and therefore have limited value in multiple level disease. Many studies have shown measurements at rest to have little value, as they may be normal in patients with arterial obstructive disease (2.23.35.37-40). It is therefore necessary to perform flow measurements during hyperemia and in chapter IV the flow values for normal persons and for patients at rest and during hyperemia have been given. Important hyperemic flow parameters, indicative of arterial obstruction, are a low peak flow, a delay in the timing of this peak flow, and a prolonged hyperemic response (1.27.38-40). Most authors agree that flow measurements during hyperemia can separate the normal from the pathological states and give a general estimation as to the functional importance of arterial obstructive disease (35.37-40), but do not provide specific information as to the localization of the hemodynamically significant lesions (41.42). There exists a relationship between the postexercise systolic blood pressures at the ankle and the calf flow values. Sumner and Strandness (41) considered pressure measurements at least as valuable as the more cumbersome flow measurements (fig. 1.2.3, chapter IV).

III.5 Pulse waveform analysis

The pulsatile inflow of blood into the leg causes synchronous changes in segmental volume, pressure and flow velocity. These periodic changes can be measured and recorded and a signal analysis performed (27).

III.5.1 Pressure waveform analysis
Bollinger et al (20) measured blood pressure directly by transcutaneous micromanometry at the ankle in healthy persons and patients, at rest and during PIRH. The continuously registrated blood pressure waveforms reflected the hemodynamic significance of stenoses and occlusions. Johnston (43) reconstructed an arterial pressure waveform of the pedal arteries from information obtained by the use of a standard blood pressure cuff, lead II of the electrocardiogram and a flow detector. Systolic, diastolic, pulse and mean arterial pressures and the rate of rise of systolic pressure were measured. He concluded that the rate of rise of the arterial pressure or the systolic pressure slope was an extremely sensitive indicator of the presence of even minor degrees of arterial narrowing. Leveson et al (44) used pressure curves to assess the aorto-iliac segment. They determined a pressure index (systolic femoral pressure/systolic aortic pressure) and a systolic slope index (femoral systolic slope/aortic systolic slope) at rest. They concluded that the systolic slope index was more sensitive in distinquishing patients from healthy persons with angiography as the goldstandard.

III.5.2 Pulse volume analysis
The volume changes of a particular segment of an extremity can be recorded with a plethysmograph. Buth (28), Hylkema (2) and Bernink (35) have given extensive reviews of current plethysmographic techniques. Oscillographic methods (Hylkema; 2) are unsuitable for waveform analysis and the mechanic devices have no longer a place in vascular diagnosis (28). The plethysmograph records limb segment volume changes with each cardiac cycle. Although the manner in which the volume changes are sensed may differ according to the type of plethysmograph, the resulting waveforms are similar in appearance (27.28). The normal pulse contour exhibits a steeply rising upslope, a fairly sharp peak and a dicrotic notch on the downslope. The downslope curves smoothly to the baseline. A mildly obstructive contour exhibits

loss of the dicrotic notch and slight bowing of the downslope away from the baseline (27.28). A moderately obstructive contour demonstrates delay in the upslope and a rounded peak in addition to the other changes (27.28). A severely obstructive contour demonstrates low amplitude and exaggeration of the above mentioned abnormalities, and there is no reaction to hyperemia (27.28). The plethysmographic method should be combined with pressure measurements to give maximal diagnostic information (28). In the assessment of the aorto-iliac segment, the volume pulses were found to be of little value by Hylkema (2). Buth (28) used the Pulse Volume Recorder (P.V.R.), an airfilled rubber cuff plethysmograph developed by Darling and Raines (45). Using P.V.R. amplitudes obtained at various levels, in combination with segmental blood pressure measurements at rest and during hyperemia, the aorto-iliac segment was correctly assessed in 70-80% of the cases. The method included a multivariant analysis of 9 different parameters and was considerable less sensitive in the case of iliac stenoses (table 1).

III.5.3 Flow velocity waveform analysis
Blood flow velocity changes can easily be detected by ultrasound Doppler examinations of the vessel. Kitslaar (26) and Bruins Slot (46) have extensively described the principles and applicability of various forms of Doppler ultrasound equipment. The advantages of the ultrasound Doppler method include non-invasiveness, wide applicability, ease of performance and relatively inexpensive equipment. The Doppler signals can be submitted to a qualitative or a quantitative analysis.

III.5.3.1 Qualitative analysis
- Acoustic Analysis (1)

The arterial Doppler signal can be recognized by two, sometimes three separate components. The first component has the highest frequency and represents the systolic acceleration of the blood flow (47). In diastole can be heard a second sound of lower frequency, representing reversed flow (48). An inconstant third component follows, consisting of even lower frequencies, representing the return of forward flow (49). During hyperemia the reversed flow component disappears and the Doppler signal is more highly pitched (50). The sound of blood flowing through a stenosis is very highly pitched during systole and of a lower than normal pitch during diastole. Behind the stenosis, the diastolic component may be absent and a resemblance with a signal obtained during hyperemia can occur (51). The quality of the acoustic Doppler signal may be graded. Bruyninckx (1) used the same four score system as Thulesius and Gjores (52). Thulesius reported poor results with the system in the evaluation of arterial obstructive disease. Bruyninckx was able to discriminate normal from obstructed vessels in 95% of cases. He found a 81% accordance between the score system and the localization and extent of obstructive lesions as seen on a angiogram. From the data of Bruyninckx the value of the score system in assessing the aorto-iliac segment can be calculated (26) (table 1). The accuracy is 84%, the sensitivity 92% and the specificity 82%.

Felix et al (53) using a four score system reported an accordance with angiography in 77%-100% of cases, depending on which vessel was being examined.

- waveform morphology analysis

This analysis requires a graphic recording of the Doppler signal as a function of time. Sophisticated equipment is needed and interpretation of results is difficult. Waveform recordings can be achieved with a frequency spectrum analysis of the Doppler signal and with a frequency to voltage converter, also known as a zero-crossing detector. Both methods have their advantages and drawbacks (54). Several classifications of the recordings have been described (26.55-60). The normal peripheral arterial Doppler waveform will exhibit multiphasic pulsatility, sharp, rapid, systolic upstroke and downstroke, and variable, diastolic, reverse flow and oscillations depending on the artery from which the recording was taken. A change of multiphasic pulsatility to monophasic or absence of pulsatility, signifies severe stenosis or occlusion proximal to the point of examination with distal flow being largely or totally supplied by collateral vessels.
Proximal stenotic disease diminishes the speed and amplitude of the systolic upstroke, causes loss of the dicrotic notch, slows the downstroke, and dampens diastolic oscillations.
Loss of reverse flow and diastolic oscillations from large peripheral vessels signifies a lack of arterial compliance due to proximal stenosis or occlusion and decreased peripheral resistance.
Proximal multiple level occlusion may result in total loss of systolic forward flow and a flat recording. Yao (57) used Doppler ultrasound waveform analysis of the pedal arteries in combination with ankle blood pressure measurements. In the assessment of the aorto-iliac segment these two methods combined were 84% accurate, 39% specific and 99% sensitive, as calculated by Kitslaar (26) from Yao's data (table 1). Thulesius (61) found his own classification unreliable in the determination of the severity of arterial obstructive disease compared with flow studies and even more unreliable in comparison with ankle blood pressure measurements. Faris and Jamieson (30) found femoral velocity patterns more reliable in assessing the aorto-iliac segment than thigh pressure measurements at rest and after exercise. They reported a high percentage of borderline blood flow velocity tracings (31%) and even abnormal tracings (14%) in patients with solitary superficial femoral lesions. This finding indicates that outflow disease as well as inflow disease influences the femoral velocity waveform.

III.5.3.2 Quantitative analysis
This form of analysis can be semi-quantitative or fully-quantitative. Quantitative measurements of the blood flow velocity in cm/sec by Doppler ultrasound require calibration and correlation studies with an electromagnetic flow meter in vitro (62.63) or knowledge of the diameter of the vessel under study (46).
The quantitative method by means of Doppler ultrasound is not really a waveform analysis but more a non-invasive way of measuring blood flow

velocity. The method is reported to have a good degree of reproducibility (62). Blood flow velocity measurements at rest have similar drawbacks in the diagnosis of arterial insufficiency, as blood flow measurements. Thus the measurements have to be performed during hyperemia. In combination with hyperemia the method allowed a limited degree of separation between aorto-iliac, femoro-popliteal and multiple level lesions, and between normal individuals and those with arterial obstructive disease (62).
The semi-quantitative parameters can be obtained by measuring several characteristics of the flow velocity waveform. Amplitude parameters such as the height of maximum positive or negative deflections of the waveform can be measured as well as time related parameters such as duration of the upstroke or downstroke of the waveform. Derivatives from these amplitude and time related parameters, such as height or time ratios, acceleration, deceleration, mean values and peak/mean values can be calculated. Many authors have reported the use of these semi-quantitative parameters in the assessment of the aorto-iliac segment (21.26.58.62-65). None of the results are very satisfactory, especially in the localization of the hemodynamically significant lesions (table 1). Most of the parameters suffer from the influence of Doppler probe to vessel angle on the waveform. In order to lessen this problem the pulsatility index (P.I.) was introduced (66-68). This is obtained by a Fourier analysis of the waveform. A Fourier analysis is a mathematical way of describing periodic phenomena (27.69). It was then shown that the basic shape of the maximum frequency envelope of a spectrum analyzed Doppler signal was unaffected by probe to vessel angle or by the flow profile (70), and the entire waveform could therefore be expressed as one parameter, the pulsatility index.
The pulsatility index is defined as the sum of the maximum oscillatory energy of the Fourier harmonics of the waveform divided by the mean energy over a cycle. Normal PI values have been reported by Gosling et al (66) for the vessels of the lower extremity. Both Harris et al (71) and Johnston et al (72) have reported good correlations of the PI with arteriographic severity gradings of arterial obstructive disease. The calculation of a Fourier PI requires sophisticated equipment, and is thus not widely applicable. A more easily obtained pulsatility index - the peak to peak PI - can be measured directly from a flow velocity waveform recording. This peak to peak PI bears a close relationship to the Fourier PI (72) and is defined as the ratio of the peak to peak distance of the curve to the mean height of the curve per cycle. A fairly good correlation between aorto-iliac angiographic gradings and the peak to peak PI of a spectrum analyzed flow velocity waveform was reported by the group of Johnston (72-74).
Although there are theoretical objections to doing so (73), some authors used the peak to peak PI, derived from the waveform of a zero-crossed femoral artery Doppler signal to assess the aorto-iliac segment (58.75). The value of the PI of the common femoral artery in the assessment of the aorto-iliac segment has been criticized in some recent reports (76.77). Both groups of investigators showed that the value of the PI in assessing the aorto-iliac segment is reduced considerably in the presence of stenoses or obstructions in the superficial femoral artery. The PI, is thus of limited value in the

presence of multiple level disease. Baird et al (77) described and tested another parameter, the L.T. factor (Laplace transform analysis factor), in the assessment of the aorto-iliac segment. The L.T. factor is derived from the femoral, Doppler derived velocity waveform. The waveform has to be expressed mathematically by a curve fitting technique (77.78). The L.T. factor is reported to be promising in assessing multiple level disease, as superficial femoral artery disease does not seem to influence the results (77.78). However, sophisticated equipment is required to calculate the L.T. factor. Kitslaar (26) studied several methods of assessing the aorto-iliac segment and arrived at some rather frustrating conclusions. He found that clinical examination (pulse palpation), segmental systolic pressure measurement and Doppler signal analysis were all of equal value. The PI (among other parameters) was excluded from further consideration when it was found in a preselection study to have very little value in the classification of lower extremities with arterial obstructive disease. With a combination of the thigh pressure index and upstroke time of the femoral Doppler signal an accuracy of 84%, a sensitivity of 83% and a specificity of 84% could be obtained in the assessment of the aorto-iliac segment, using angiography as the standard for comparison. Kitslaar did not study direct (intra-arterial) femoral artery blood pressures.

According to many investigators (chapter VIII, IX and III.3.2) direct femoral pressure studies at rest and during hyperemia are superior to any other, currently available method in assessing the aorto-iliac segment and should be used as the goldstandard for the comparison of other diagnostic methods (79.80). Flanigan et al (34.80-82) evaluated the techniques of Doppler waveform analysis, femoral artery PI, high thigh pressures and femoral artery pulse palpation and found them to correlate poorly with common femoral intra-arterial pressure measurements. Table 1 summarizes the results of several methods commonly used to assess the aorto-iliac segment. The figures should be interpreted with caution as parameter thresholds, goldstandards and patient populations were often incomparable.

Author	Diagnostic Method	Goldstandard	Acc %	Sens %	Spec %	PPV %	NPV %	Agreement with goldstandard %
Brener et al '74	femoral pulse palpation	FAP with PIRH	-	-	-	-	-	unsatisfactory
Brewster et al '79	femoral pulse palpation	FAP with PIRH	-	-	-	-	-	64-73
Flanigan et al '82	femoral pulse palpation	FAP with PRH	-	-	-	-	-	unsatisfactory
Brewster et al '79	angiography	FAP with PIRH	-	-	-	-	-	35-69
Brener et al '74	angiography	FAP with PIRH	-	-	-	-	-	unsatisfactory
Flanigan et al '84	triplane angiography	postoperative results	80	88	76	90	70	-
Hylkema '75	thigh pressures	angiography	80	90	73	-	-	-
Faris/Jamieson '75	thigh pressures	angiography	61	93	46	-	-	-
Heintz et al '78	* thigh pressures (cuff 19 cm)	angiography	83	95	74	-	-	-
	* thigh pressures (cuff 8 cm)	angiography	91	95	89	-	-	-
	* high thigh/low thigh pressure combination	angiography	96	95	96	-	-	-
Masafumi Hirai/ Schoop '84	post exercise thigh pressure	angiography	93	95	91	85	97	-
Bruyninckx '76	thigh/ankle pressure combination	angiography	94	82	97	-	-	-
Flanigan et al '81	high thigh pressures (wide cuff)	FAP	63	79	56	-	-	-
Buth '78	thigh pressures/PVR combination	angiography	-	-	In case of multiple level disease			59-93
					in case of solitary aorto-iliac disease			65-88
Bruyninckx '76	Doppler "Sonoscore"	angiography	84	92	82	-	-	-
Yao '70	postexercise ankle pressure/QDWA of pedal arteries combination	angiography	84	99	39	-	-	-
Fronek et al '78	* thigh pressures	angiography	-	68	-	-	-	-
	* thigh pressure/ SQDWA combination	angiography	-	96	-	-	-	-
Kitslaar '82	thigh pressure/SQDWA combination	angiography	84	83	84	-	-	-
Nicolaides et al '76	SQDWA (multivariate analysis)	angiography	-	-	-	-	-	86
Baird et al '80	* L.T. factor	angiography	-	85	84	-	-	-
	* P.I.	angiography	-	41	90	-	-	-
Brener et al '74	FAP with PIRH	postoperative results	-	-	-	-	-	>90
Brewster et al '79	FAP with PIRH	postoperative results	-	-	-	-	-	96 †
Flanigan et al '83	FAP with PRH (retrospective study)	postoperative results	95	88	100	-	-	-
Flanigan et al '84	FAP with PRH (prospective study)	postoperative results	98	94	100	100	98	-

Table I: Summary of the results of several diagnostic methods in the assessment of aorto-iliac arterial obstructive disease.
†In case the FAP parameter was positive as to the aorto-iliac disease.

Legend:
FAP = direct femoral artery pressure measurement.
PIRH = post-ischemic reactive hyperemia.
PRH = papaverine reactive hyperemia.
QDWA = qualitative Doppler waveform analysis.
SQDWA = semi-quantitative Doppler waveform analysis of the femoral artery.
LT factor = Laplace transform analysis factor.
PI = pulsatility index.
Acc = accuracy
Spec = specificity
Sens = sensitivity
PPV = positive predictive value.
NPV = negative predictive value.

1. Bruyninckx C.M.A.
Pre- en postoperative evaluatie van claudicatio intermittens met behulp van een Doppler-flowmeter.
Thesis, Nijmegen 1976

2. Hylkema B.S.
Tussen polspalpatie en aortografie.
Diagnostische betekenis van enkele onbloedige methoden bij ontoereikende bloedvoorziening van de benen.
Thesis, Groningen 1975

3. Wesolowski S.A., Martinez A., Domingo R.T., et al
Indications for aorto-femoral arterial reconstruction: A study of borderline risk patients.
Surgery 1966; 60: 288-298

4. Darling R.C., Brewster D.C., Hallett J.W.,
Aorto-iliac reconstruction.
Surg. Clin. North Am. 1979; 59: 565-579

5. Rutherford R.B.
Vascular Surgery.
W.B. Saunders Co. Philadelphia 1977

6. Sanchez S.A.
Strain gauge plethysmography. A diagnostic aid in obstructive arterial disease.
Postgrad. Med. 1966; 39: 451

7. DeWeese J.A., van de Berg L., May A.G., Rob C.G.
Stenoses of arteries of the lower extremity.
Arch. Surg. 1964; 89: 806

8. Carter S.A.
Response of ankle systolic pressure to leg exercise in mild or questionable arterial disease.
New Engl. J. Med. 1972; 287: 578

9. Brener B.J., Raines J.K., Darling R.C., Austen W.G.
Measurement of systolic femoral arterial pressure during reactive hyperemia. An estimate of aorto-iliac disease.
Circulation 1974; 49-50 suppl. II: 259

10. Gupta T.C., Wiggers C.J.
Basic hemodynamic changes produced by coarctation of different degrees.
Circulation 1951; 3: 17

11. Wylie E.J., McGuinness J.S.
The recognition and treatment of arteriosclerotic stenosis of major arteries.
Surg. Gynecol. Obstet. 1953; 97: 425

12. Terpstra J.L.
De chirurgische reconstructietherapie bij arterieel obliterend vaatlijden.
Thesis, Leiden 1960

13. Szilagyi D.E., Smith R.F., Macksood A.J., Eyler W.R.
Abdominal aortography. Its value and its hazards.
Arch. Surg. 1962; 85: 41

14. Lang E.K.
Complications of retrograde percutaneous arteriography.
J. Urol 1963; 90: 604

15. John H.T., Warren R.
The stimulus to collateral circulation.
Surgery 1961; 49: 14

16. Rottier A.B., Vosmer A.M.
Onderbeenamputaties voor ischemisch gangreen. De betekenis van de arteriografische gegevens.
Ned. T. Geneesk. 1975; 119: 781

17. Koontz T.J., Stansel H.C.
Factors influencing patency of the autogenous vein-femoropopliteal bypass graft: an analysis of 74 cases.
Surgery 1972; 71: 753

18. Miller V.M.
Femoropopliteal bypass graft patency: an analysis of 156 cases.
Ann. Surg. 1974; 180: 35

19. Grüntzig A., Brunner U., Meier W., Bollinger A.
Prä- und postoperative Messung der systolischen Knöchelarteriendrucke mit Doppler-Ultraschall.
In: Messmethoden bei arteriellen Durchblutungsstörungen (Aktuelle Probleme in der Angiologie, 13).
H. Huber, Bern 1971; 177.

20. Bollinger A., Barras J.D., Mahler F.
Measurement of foot artery blood pressure by micromanometry in normal subjects and in patients with arterial occlusive disease.
Circulation 1976; 53: 506

21. Myhre H.O.
Reactive hyperemia of the human lower limb.
Measurement of postischemic blood flow velocity in controls and in patients with lower limb atherosclerosis.
VASA 1975; 4: 145-149

22. Bienmüller H.
Frühdiagnostiek obliterierender Gefässerkrankungen der unteren Gliedmasen.

Wertigkeit verschiedenen unblutigen apparativer untersuchungsverfahren.
Med. Klin. 1975; 70: 1139-1147

23. Bollinger A., Mahler F., Zehender O.
Kombinierte Druck- und Durchflussmessungen in der Beurteilung arteriellen Durchblutungsstörungen.
Dtsch. Med. Wschr. 1970; 95: 1039-1043

24. Yao S.T., Needham T.N., Gourmoos C., Irvine W.T.
A comparative study of strain-gauge plethysmography and Doppler ultrasound in the assessment of occlusive arterial disease of the lower extremities.
Surgery 1972; 71: 4-9

25. Pearce W.H., Yao J.S.T., Bergan J.J.
Non-invasive vascular diagnostic testing.
Current problems in Surgery 1983; 20: 461-538

26. Kitslaar P.J.E.H.M.
Doppler ultrasound tests in the diagnosis of chronic aorto-iliac obstruction.
Thesis, Maastricht 1982

27. Strandness D.E., Sumner D.S.
Hemodynamics for surgeons.
Grune & Stratton, New York 1975

28. Buth J.
Het vasculaire laboratorium.
Thesis, Amsterdam 1978

29. Heintz S.E., Bone G.E., Slaymaker E.E. et al
Value of arterial pressure measurements in the proximal and distal part of the thigh in arterial occlusive disease.
Surg. Gynecol. Obstet. 1978; 146: 337-343

30. Faris I.B., Jamieson C.W.
The diagnosis of aorto-iliac stenosis. A comparison of thigh pressure measurement and femoral artery flow velocity profile.
J. Cardiovas. Surg. 1975; 16: 597-602

31. Hurlow R.A., Chandler S.T., Hardman J., Strachan C.J.L.
The non-invasive assessment of aorto-iliac disease: a comparison of dynamic angiology with thigh/brachial pressure index.
Surgery 1978; 84: 278-282

32. Cutajar C.L., Marston A., Newcombe J.F.
Value of cuff occlusion pressures in assessment of peripheral vascular disease.
Br. Med. J. 1973; 2: 392-395

33. Fronek A., Coel M., Bernstein E.F.
The importance of combined multisegmental pressure and Doppler flow velocity studies in the diagnosis of peripheral arterial occlusive disease.
Surgery 1978; 84: 840-847

34. Flanigan D.P., Gray B., Schuler J.J. et al
Correlation of Doppler - derived high thigh pressure and intra-arterial pressure in the assessment of aorto-iliac occlusive disease.
Br. J. Surg. 1981; 68: 423-425

35. Bernink P.J.L.M.
Parameters van de circulatie in de onderste extremiteiten met betrekking tot atherosclerosis obliterans.
Thesis, Groningen 1978

36. Masafumi Hirai, Schoop W.
Hemodynamic assessment of the iliac disease by proximal thigh pressure and Doppler femoral flow velocity.
J. Cardiovasc. Surg. 1984; 25: 365-369

37. Strandell T., Wahren J.
Circulation in the calf at rest, after arterial occlusion and after exercise in normal subjects and in patients with intermittent claudication.
Acta Med. Scand. 1963; 173: 99-105

38. Hillestad L.K.
The peripheral blood flow in intermittent claudication V plethysmographic studies. The significance of the calf blood flow at rest and in response to timed arrest of the circulation..
Acta Med. Scand 1963; 174: 23-41

39. Siggaard-Andersen J.
Obliterative vascular disease. Classification by means of the Dohn plethysmograph.
Acta Chir. Scand. 1965; 130: 190-198

40. Dahn J.
On clinical use of venous occlusion plethysmography of calf. II Results in patients with arterial disease.
Acta Chir. Scand. 1965; 130: 61-75

41. Sumner D.S., Strandness D.E.
The relationship between calf blood flow and ankle blood pressure in patients with intermittent claudication.
Surgery 1969; 65: 763-771

42. Lewis J.D., Papathanaiou C., Yao S.T., Eastcott H.H.G.
Simultaneous flow and pressure measurements in intermittent claudication.

Br. J. Surg. 1972; 59: 418-422

43. Johnston K.W.
Systolic slope and other pressure measurements in patients with peripheral vascular disease.
Surg. Gynecol. Obstet. 1975; 140: 249-251

44. Leveson S.H., Guillou P.J., Terry H.J. et al
Pulse pressure wave analysis in the diagnosis of aorto-iliac disease.
Ann. Surg. 1978; 187: 161-165

45. Raines J.K., Darling R.C., Buth J. et al
Vascular laboratory criteria for the management of peripheral vascular disease of the lower extremities.
Surgery 1976; 79: 21-29

46. Bruins Slot H.
Doppler studies in the femoro-popliteal pathway.
Thesis, Maastricht 1981

47. Strandness D.E., Sumner D.S.
Non-invasive methods of studying peripheral arterial function.
J. Surg. Res. 1972; 12: 419

48. Strandness D.E., Kennedy J.W., Judge T.P., McLeod F.D.
Transcutaneous directional flow detection: a preliminary report.
Amer. Heart J. 1969; 78: 65

49. Yao S.T., Hobbs J.T., Irvine W.T.
Pulse examination by an ultrasonic method.
Brit. Med. J. 1968; 4: 555

50. Brunner H.H., Bollinger A., Anliker M. et al
Bestimmung instantaner strömungsgeschwindigkeitsprofile in der A. femoralis communis mit gepulstem Doppler-Ultrashall bei stenosen und Verschüssen der Beckenarterien.
Dtsch. Med. Wschr. 1974; 99: 3

51. Allan J.S., Terry H.J.
The evaluation of an ultrasonic flow detector for the assessment of peripheral vascular disease.
Cardiovasc. Res. 1969; 3: 503

52. Thulesius O., Gjöres J.E.
Use of Doppler shift detection for determining peripheral arterial blood pressure.
Angiology 1971; 22: 594

53. Felix W.R., Sigel B., Popky G.L.
Doppler ultrasound in the diagnosis of peripheral vascular disease.
Semin Roentgenol. 1975; 10: 315-321

54. Reneman R.S., Spencer M.P.
Difficulties in processing of an analogue Doppler flow signal with special reference to zero-crossing meters and quantification. In: Cardiovascular applications of ultrasound.
North Holland Publishing Co., Amsterdam 1974.

55. Barnes R.W., Wilson M.R.
Doppler ultrasonic evaluation of peripheral arterial disease.
A programmed audiovisual Instruction, Iowa 1976

56. Yao Y.S.T., Bergan J.J.
Application of ultrasound to arterial and venous diagnosis.
Surgical Clinics of North America, 1974; 54: 23-38

57. Yao J.S.T.
Haemodynamic studies in peripheral arterial diseases.
Brit. J. Surg. 1970; 57: 761-766

58. Nicolaides A.N., Gordon-Smith J.C., Dayandas J., Eastcott H.H.C.
The value of Doppler blood flow velocity tracings in the detection of aorto-iliac disease in patients with intermittent claudication.
Surgery 1976; 80: 774-778

59. Barnes R.W.
Non-invasive diagnostic techniques in peripheral vascular disease.
Medical college of Virginia, Richmond 1980

60. Strandness D.E., McCutcheon E.P., Rushmer R.F.
Application of a transcutaneous Doppler flowmeter in evaluation of occlusive arterial disease.
Surg. Gynecol. Obstet 1966; 122: 1039-1045

61. Thulesius D.
Beurteilung des Schweregrades arterieller Durchblutungsstörungen mit dem Doppler - Ultrashall - Gerät.
In: Messmethoden bei arteriellen Durchblutungsstörungen.
H. Huber, Bern 1971; 44-57

62. Fronek A., Coel M., Bernstein E.T.
Quantative ultrasonographic studies of lower extremity flow velocities in health and disease.
Circulation 1976; 53: 957-960

63. Bernstein E.F., Murphy A.E., Shea M.A., Housman L.B.
Experimental and clinical experience with transcutaneous Doppler ultrasonic flowmeters.
Arch. Surg. 1970; 101: 21-25

64. Rittenhouse E.A., Strandness D.E.
Oscillatory flow patterns in patients with aorto valve disease.
Am. J. Cardiol 1971; 28: 568-574

65. Humphries K.N., Hames T.K., Smith S.W.J. et al
Quantitative assessment of the common femoral to popliteal arterial segment using continuous wave Doppler ultrasound.
Ultrasound Med. Biol. 1980; 6: 99-105

66. Gosling R.G., Dunbar G., King D.H. et al
The quantitative analysis of occlusive peripheral arterial disease by a non-intrusive ultrasonic technique.
Angiology 1971; 22: 52-55

67. Woodcock J.P., Gosling R.G., Fitzgerald D.E.
A new non-invasive technique for assessment of superficial femoral artery obstruction.
Br. J. Surg. 1972a; 59: 226-231

68. Gosling R., King D., Woodcock J.
Blood-velocity waveforms in the evaluation of atheromatous changes.
In: Blood flow measurement Sector, London 1972: 33-36

69. McDonald D.A.
Blood flow in arteries.
Williams & Wilkins Co., Baltimore 1974

70. Woodcock J. Gosling R., King D., Newman D.
Physical aspects of blood-velocity measurement by Doppler shifted ultrasound.
In: Blood flow measurement Sector, London 1972b: 19-23

71. Harris P.L., Taylor L.A., Cave F.D., Charlesworth D.
The relationship between Doppler ultrasound assessment and angiography in occlusive arterial disease of the lower limbs.
Surg. Gynecol. Obstet 1974; 138: 911-914

72. Johnston K.W., Maruzzo B.C., Taraschuk I.
Fourier and peak to peak pulsatility indices in arterial occlusive disease.
In: Non-invasive clinical measurement.
Pitman Medical, Turnbridge Wells, 1977; 98-104

73. Johnston K.W., Maruzzo B.C., Cobbold R.S.C.
Errors and artifacts of Doppler flow-meters and their solution.
Arch. Surg. 1977; 112: 1335-1342

74. Johnston K.W., Taraschuk I.
Validation of the role of pulsatility index in quantitation of the severity of peripheral arterial occlusive disease.
Am. J. Surg. 1976; 131: 295-297

75. Aldstaedt F., Storz L.W., Rückert U.
Erste Erfahrungen mit einer semiquantitativen Analyse von Doppler-Fluss-Kurver in der Gefässchirurgie.
In: Ultrashall-Doppler-Diagnostik in der Angiologie.

Thieme, Stuttgart 1979; 67-79

76. Ward A.S., Martin T.P.
Some aspects of ultrasound in the diagnosis and assessment of aorto-iliac disease.
Am. J. Surg. 1980; 140: 260-265

77. Baird R.N., Bird D.R., Clifford D.C. et al
Upstream stenosis. Its diagnosis by Doppler signals from the femoral artery.
Arch. Surg. 1980; 115: 1316-1322

78. Skidmore R., Bird D.R., Woodcock J.P. et al
Transfer function analysis of common femoral artery Doppler waveforms.
Br. J. Surg. 1979; 66: 883

79. Flanigan D.P., Williams L.R., Schwartz J.A. et al
Hemodynamic evaluation of the aorto-iliac system based on pharmacologic vasodilatation.
Surgery 1983; 93: 709-714

80. Flanigan D.P., Ryan T.J., Williams L.R. et al
Aorto-femoral or femoro-popliteal revascularization. A prospective evaluation of the papaverine test.
J. Vasc. Surg. 1984; 1: 215-223

81. Flanigan D.P., Collins J.T., Schwartz J.A. et al
Hemodynamic and arteriographic evaluation of femoral pulsatility index.
J. Surg. Res. 1982; 32: 234-238

82. Flanigan D.P., Collins J.T., Goodreau J.J. et al
Femoral pulsatility index in the evaluation of aorto-iliac occlusive disease.
J. Surg. Res. 1981; 31: 392-399

CHAPTER IV

METHODS OF INDUCING REACTIVE HYPEREMIA AND THE EFFECT ON BLOOD FLOW AND BLOOD PRESSURE.

IV.1 Introduction

From the basic hemodynamic principles, outlined in chapter II, it is apparent that vascular diagnostic tests need to be performed both at rest and during reactive hyperemia (RH).
In this chapter the different types of RH and their effect on blood flow and blood pressure will be discussed. RH is defined as the increase of blood flow in an organ or part of the body above the resting level as a reaction to a local stimulus. This stimulus may by high levels of physical work (post-exercise reactive hyperemia, PERH), a period of total ischemia (post-ischemic reactive hyperemia, PIRH) or RH can be induced by pharmacological agens (pharmacological reactive hyperemia, PRH).

IV.2 Post-exercise Reactive Hyperemia (PERH)

IV.2.1 Genesis of PERH

Because it is easier to measure blood flow and -pressure after the cessation of exercise than during exercise, it is usual to study the hemodynamic changes in the post-exercise period.
Barcroft et al (1.2) studied blood flow during tetanic and rhythmic contractions. During heavy tetanic contractions blood flow does not increase (1). During rhythmic contractions the increase of blood flow takes place mainly during relaxation periods (2). The period after sustained exercise is such a relaxation period during which blood flow increases. Bernink (3) reported a good correlation between blood flow velocity (measured by Doppler ultrasound) during a relaxation period and the flow velocity measured immediately after cessation of exercise. Haddy and Scott (4.5.6) have given excellent reviews about the genesis of PERH. Their studies indicated that metabolic factors are involved in the genesis of PERH. Over the years many factors have been implicated in inducing PERH. The most important of these are: Oxygen, Hydrogen, Potassium, Adenine nucleotides, Adenosine and blood osmolality. These causative factors do no necessarily operate simultaneously and possibly the exact mechanism of PERH is multicausal. It has been shown that certain combinations of factors produce a greater change in resistance than occurs with any one factor (4). Bayliss introduced the myogenic theory in 1902 (7), which states that vasodilatation occurs when the transmural pressure has been reduced. This is the case when extraluminal pressure is raised by muscular contraction or when the intraluminal pressure is decreased as during ischemia. It may be that certain factors, such as potassium and osmolality initiate PERH and others, such as oxygen and hydrogen, maintain it with the Bayliss mechanism participating throughout the

exercise.

IV.2.2 PERH tests

Any form of muscular exercise will induce PERH and can theoretically be employed in a diagnostic test. For practical reasons only those which can be performed in a laboratory setting are used. Many efforts have been dedicated to the standardization of exercise conditions and different tests have been introduced. These exercise tests include: bicycle ergometry (8), pedal ergometry (9), tip-toe exercise (10), step-up tests (11). Walking is a form of exercise that people are accustomed to. A free-walking test, however, requires considerable space to perform so the treadmill test is most often chosen (12-14). The patient performs standardized work and the relative claudication or walking time (time until pain starts), and the claudication time (time until exercise has to be stopped because of pain) can be measured (14). Many authors have tried to find a correlation between ankle blood pressures or blood flow parameters of the calf, and the treadmill claudication time. Yao et al (15), Bollinger et al (16) and Lorentsen (17) found some correlation whilst Hylkema (9) found none. Hylkema (9) was also unable to find a correlation between anamnestic claudication time and relative treadmill claudication time. The reproducibility of the walking test is poor (18). Hillestad found an individual variation coefficient of 31.2% for the treadmill test (19). The main limitation of exercise tests is that the results are very dependent on the occurrence of and the timing of onset of pain - parameters requiring a subjective assessment by the patient (16). Rigid standardization only partly compensates for the errors introduced by variations in the patients assessment of pain. Other influencing factors are: walking technique (16), training (16), body weight (19) and patient-motivation (20).

IV.2.3 The influence of PERH on blood flow and -pressure

IV.2.3.1 PERH in normal extremities

Moderate exercise normally increases total leg blood flow five to ten times (21.22). Flow under resting conditions is 300-400 ml/min (23-25). Muscle blood flow rises to 30 $\pm$ 14 ml/100ml/min during moderate exercise, reaching 70 ml/100ml/min during strenuous exercise (21). The value under resting conditions has an average of 3.5 ml/100ml/min (26).

Upon cessation of exercise, blood flow falls rapidly in an exponential fashion, reaching pre-exercise levels within one to five minutes (27). The blood pressure drop along normal arteries from the heart to the ankle is only a few mm Hg (27). At rest, ankle systolic pressures exceed the brachial systolic pressure by about 10% (27). Moderate exercise produces little or no drop in peripheral pressure at ankle level. With strenuous exercise, the pressure may fall a few mm Hg, but rapidly recovers within a minute (27).

IV.2.3.2 PERH in extremities of patients with arterial obstructive disease

Many authors have reported on the reaction of blood flow and blood

pressure in the leg with arterial obstructive disease during and after exercise (16.28-30).
In the Dutch literature this subject received much attention (theses of Barendsen, Bernink, Hylkema, Bruyninckx, Buth, Kitslaar (3.9.14.31-33)).
The main purpose of these studies was to find relationship between post-exercise changes in blood pressure and -flow, and the level of the occlusive disease and patient symptomatology. Although blood flow increases during exercise in limbs with arterial obstructive disease, the increase is far less than that observed in normal limbs undergoing similar stress (21.22). After cessation of exercise, the hyperemia is greatly prolonged, subsiding to normal levels in a logarithmic fashion over a 4 to 30 minute period (28); type I response (fig. 1).

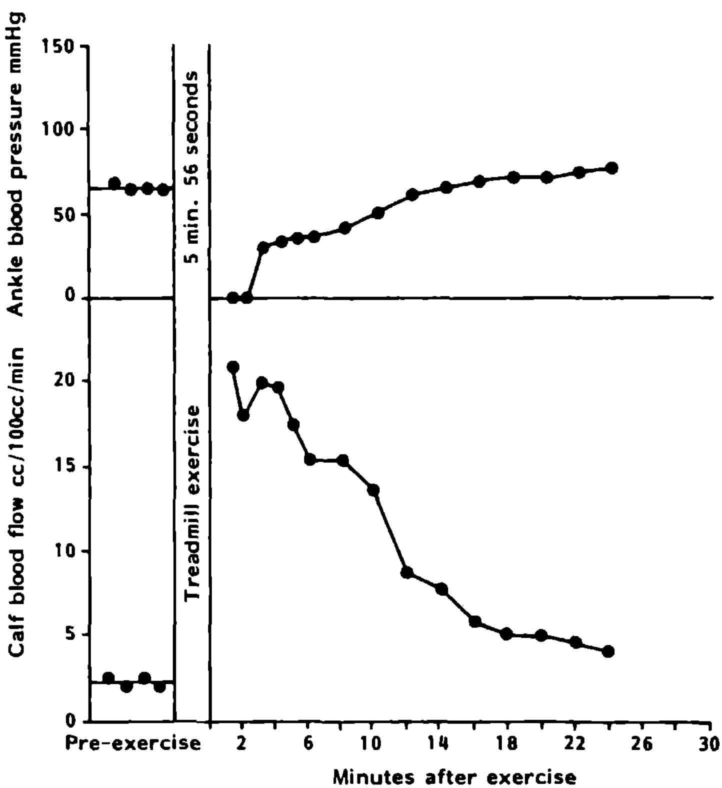

Figure 1. Pre- and postexercise ankle pressure and calf blood flow relationships in a patient with an occlusion of the common iliac artery. Type I response.

Redrawn from Sumner D.S., Strandness E.D. Jr.: Surgery 1969; 65, 763-771).

In limbs with multiple-level disease, the peripheral blood flow after exercise increases only slightly. Flow then rises further for several minutes to a peak level, before falling gradually to pre-exercise levels; type II response (fig. 2).

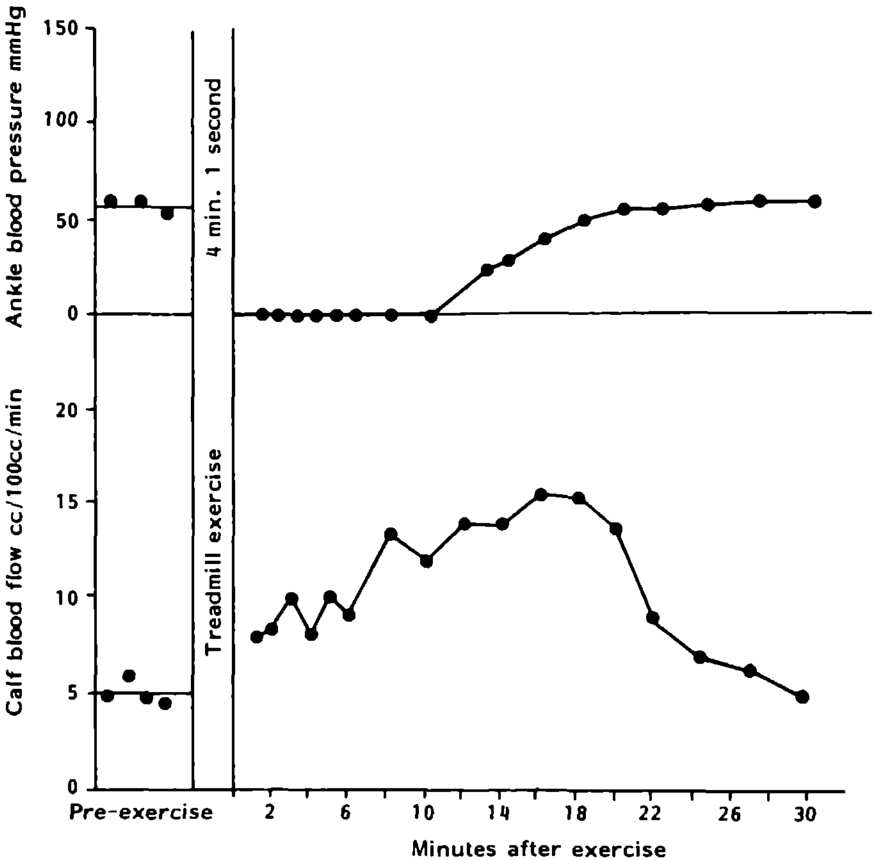

Figure 2. Pre- and postexercise ankle pressure and calf blood flow relationships in a patient with stenosis of the iliac artery and occlusion of the superficial femoral artery. Type II response.

Redrawn from Sumner D.S., Strandness E.D. Jr.: Surgery 1969; 65, 763-771).

In patients with rest pain, the first flow after exercise may even be below the resting level. The peak flow during hyperemia is quite low and delayed, with the hyperemia persisting for many minutes; type III response (fig. 3).

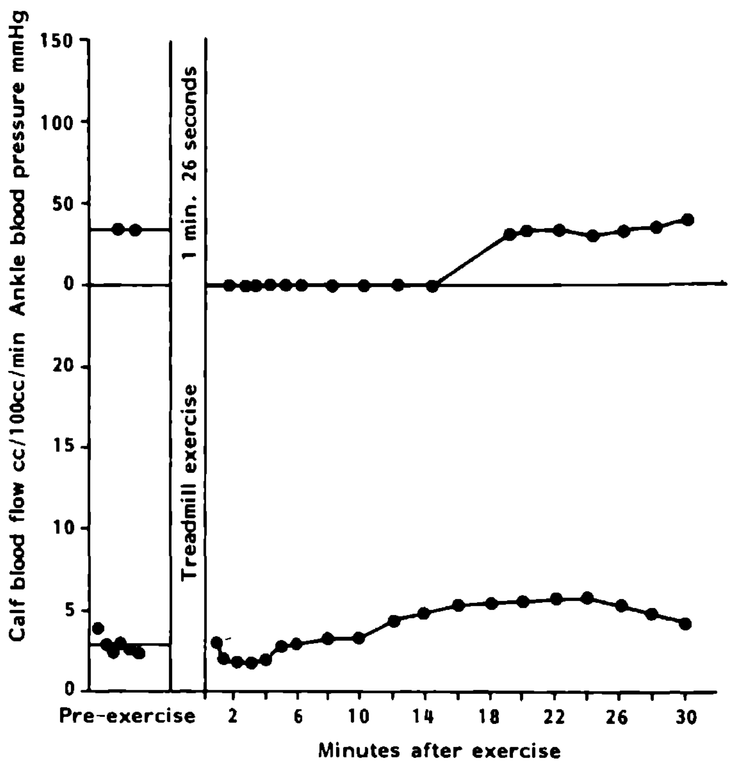

Figure 3. Pre- and postexercise ankle pressure and calf blood flow relationships in a patient with moderate rest pain and severe claudication. The iliac, common femoral, and superficial femoral arteries were occluded. Type III response.

Redrawn from Sumner D.S., Strandness D.E. Jr.: Surgery 1969; 65, 763-771).

When the blood flow to an extremity is increased following exercise, there is a marked fall in blood pressure distal to an arterial lesion. Recovery to pre-exercise levels requires a period of usually 10 to 30 minutes (27) (fig. 1.2.3.). By studying pressure and/or flow after exercise, several types of responses have been described which depend on the severity of disease and the localization of hemodynamically significant lesions.

Sumner and Strandness (28) described 3 types of calf flow and ankle pressure responses (fig. 1.2.3). Yao (29) described 4 types of flow and pressure responses. Gay and Roberts (30) reported 9 types of blood pressure response to exercise and finally Bernink (3) described 3 types of flow response, quite similar to the 3 types of Sumner and Strandness.

Figure 4 illustrates the effect of exercise on pressure-flow relationships in limbs with multiple-level obstructions.

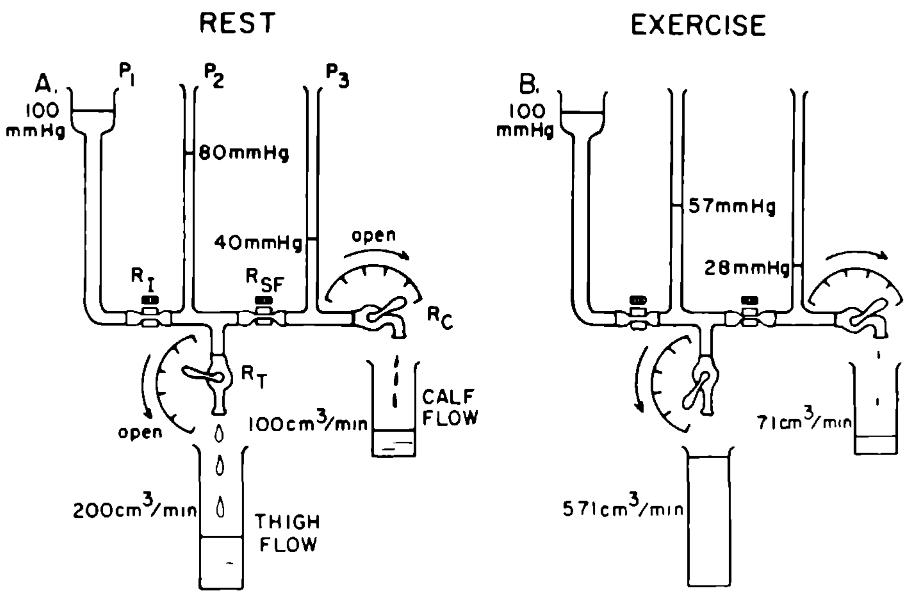

Figure 4. Hydraulic model illustrating effect of multiple level arterial obstructive disease. See text for explanation.

Redrawn from Rutherford R.B.: "Vascular Surgery", W.B. Saunders, Philadelphia, London, Toronto, 1977, figure 4-18.

In this example the iliac obstruction is represented by resistance Rl and the femoral obstruction by resistance Rsf. The variable resistances imposed by the peripheral vascular beds of the thigh and calf are represented by Rt and Rc respectively.
Blood flow at rest is being kept normal by complete vasodilatation in the calf and partial vasodilatation in the thigh. During exercise the vasodilatation in the thigh becomes complete as well (Rt open maximally, fig. 4b). Because total peripheral resistance is now reduced, blood flow through the proximal resistance Rl increases, leading to a further drop in pressure P2. Since the series of resistances leading to the calf have not changed (Rsf+Rc) and since the pressure head (P2) perfusing the calf falls, blood flow to the calf decreases.
Thus the effect of exercise is to increase flow to the thigh followed by a decrease in flow to the calf and a decrease in peripheral blood pressure. In this way the proximal vascular bed steals blood from the distal. Calf blood flow will increase only when the thigh blood flow decreases, allowing the distal blood pressure (P3) to rise. This steal phenomenon explains the type II and III responses described by Sumner and Strandness (fig. 2 and 3).

IV.3 Post-ischemic reactive hyperemia (PIRH)

IV.3.1 Genesis of PIRH

PIRH has been described as early as 1872 (Cohnheim; 34), 1878 (Lord Lister; 35), 1879 (Ray and Brown; 36), 1880 (Gaskell; 37) and 1897 (Bier; 38). PIRH can be observed in many organs and parts of the body (39) and is defined as the increased flow in response to a sudden restoration of arterial inflow after a period of cessation of this inflow (40). Many different theories have been proposed to explain this phenomenon.
Bayliss introduced the myogenic theory in 1902 (7.41). It states that the muscular wall of an artery or an arteriole undergoes relaxation when the transmural pressure is reduced. Conversely, the muscular wall contracts when the transmural pressure increases. This response is independent of any neurogenic influence. Bayliss observed the reaction even after very short occlusion times, and thus concluded that metabolic causes played no role, the origin of the response being purely myogenic.
Many investigators have supported the Bayliss theory (42-47) whilst others have not (48-50).
Another theory to explain the genesis of PIRH is the metabolic theory (4.37.48.51-54). During ischemia, when the vasodilatation occurs (36), accumulating metabolites or other substances could be responsible for PIRH. It is also possible that the lack of certain products, during ischemia, causes PIRH (55), although some hold this mechanism to be unlikely (48). Many different substances have been proposed as causative factors for PIRH, including: oxygen, histamine, ATP, bradykinin, noradrenaline, adrenaline. Histamine or H substance has been considered as being a causative factor by Lewis (56) and later by Barsoum and Smirk (57).
Other studies have not supported this concept (58-62). ATP

(adenosine-triphosphate) has been found in the venous effluent after very long occlusions (30 minutes) (63) and ATP is known to cause vasodilatation (62). Bradykinin, injected intraarterially, causes a response bearing some similarity to PIRH (64). Dornhorst (65) therefore concluded that Bradykinin could be responsible for PIRH. Abrams et al (55) suggested depletion of noradrenaline depots in the vascular wall as the cause of PIRH. Many authors (66-69) reported strong evidence for oxygen demand being the major factor causing PIRH. A neurogenic cause for PIRH was suggested (70-72) but Folkow (44) provided enough evidence to discount this theory. As in the genesis of post-exercise hyperemia, a multifactorial origin of PIRH seems most likely. The factors involved probably do not act simultaneously. The Bayliss mechanism may play a role in the early phase of the PIRH reaction provided the occlusion time is not too long; from seconds to 3 minutes depending on the resting blood flow (73.74). With longer occlusion times metabolic factors probably become more important (74). The exact nature of these metabolites remains unknown.

IV.3.2 The PIRH test

Based on the work of Patterson and Whelan (75), Lewis and Grant (48), and Eichna and Wilkins (76) an occlusion time of minimally 3 minutes has to be chosen for a clinically useful and reproducible PIRH reaction. Patterson and Whelan, and Lewis and Grant showed that the maximal vasodilatation occurring after 3 minutes occlusion reaches 80% of the vasodilatation seen after 15 minutes occlusion. The technical performance of a PIRH test is described in chapters V and VI. The major factors influencing the PIRH reaction are: the degree of obstructive disease in the arterial tree (chapter IV.3.3), the systemic systolic blood pressure (76.77), the resting blood flow (51.73) and the occlusion time (48.75).
Factors of less importance are venous congestion (46-48) and temperature (76.78). The occlusion time should be between 3 and 5 minutes, the temperature of the room constant and the venous system of the leg emptied by elevation before inflating the thigh tourniquet. The influence of different blood pressures and blood flows can make comparisons of the PIRH parameters between individuals difficult, but with standardization the variations are not great (chapter IV.3.3.1). Finally, it is important that the first blood flow or blood pressure recordings are obtained in the first few seconds after tourniquet release and then at 15-20 second intervals for 2 minutes (27). The entire PIRH reaction takes place in a shorter time period than a PERH reaction.

IV.3.3 The influence of PIRH on blood flow and blood pressure

IV.3.3.1 Introduction

PIRH has been shown to occur in both skin and muscle (26.48). As in the PERH reaction, there is a correlation between ankle blood pressure and calf blood flow during PIRH (28.79). Thus the same pressure/flow patterns as were described for PERH (fig. 1.2.3) can be expected for PIRH. The reproducibility of a PIRH test is good (26.76.80.81).

IV.3.3.2 PIRH in normal extremities

The resting blood flow in the muscles of the leg is approximately 3.5 ml/100ml/min (26.80). Immediately after tourniquet release the blood flow rises to a maximum of 25-35 ml/100ml/min (26.76.80.81) (fig. 5, curve 1).

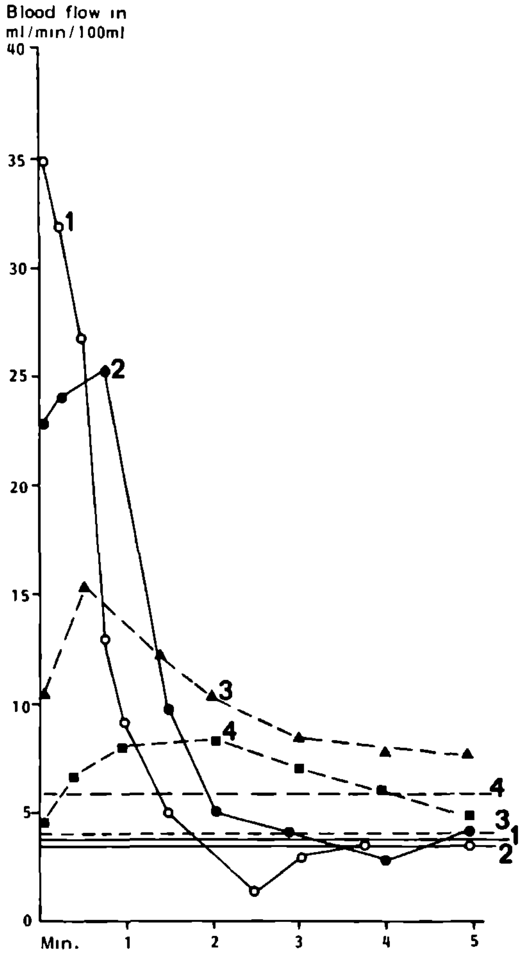

Figure 5. The hyperemic flow of the calf following 5 minutes of circulatory arrest at various stages of obliterative arterial disease. 1, Normal circulation, 2, occlusion of the femoral artery with excellent collateral flow, 3, occlusion of the femoral artery and marked stenosis of the popliteal artery, 4, occlusion of the femoral artery, marked stenosis of the popliteal artery, and marked involvement of the crural arteries. Note that in this case the initial flow is less than the resting flow and that the hyperemia is considerably delayed.

Redrawn from Rutherford R.B. "Vascular Surgery", W.B. Saunders, Philadelphia, London, Toronto, 1977, figure 8-3.

The maximum blood flow after PIRH is approximately the same as the maximum blood flow occuring after moderate exercise (chapter IV.2.3.1). After this maximal increase, a gradual fall to pre-ischemic levels (sometimes with a short "negative" phase) occurs over approximately 2 minutes (fig. 5, curve 1). The ankle blood pressure after tourniquet release has an inverse relation to blood flow velocity (79). A drop in blood pressure is observed immediately after arterial inflow has been restored. This pressure drop varies from 40% to 17% in different studies (82-86) and subsides over 15 to 30 seconds (79.82). The pressure drop also occurs during PERH and can be observed as a normal response, particularly after strenuous exercise (79).

IV.3.3.3 PIRH in extremities of patients with arterial obstructive disease.

As with the PERH studies, correlations between post-ischemic pressure/flow patterns and the extent of arterial obstructive disease were sought during PIRH (3.9.26.76.80.81.87.88). The pressure/flow patterns found in PIRH are quite similar to the patterns in PERH (80) (fig. 5). The essential features are a delay in the timing of the maximal flow and this maximal flow is less than that found in normal individuals. In severe cases of obstructive disease the initial flow after restoration of inflow (first flow) may be lower than the pre-ischemic value (27) (fig. 5). The first flow is sometimes used for diagnostic purposes buth the maximal flow is the most valuable parameter (26). In normal individuals the first flow is the same as maximal flow but in patients with obstructive disease this is not the case and maximal flow is delayed. The maximal flow in the patients varies from 16 to 160 cc/liter/min (= 1.6 - 16 cc/100cc/min). Hillestad (26) stated that a maximal flow less than 15 cc/100cc/min is abnormal for the lower extremities. Several authors (3.9.26.80.81.87.88) found a correlation between extent of the arterial obstructive disease and values of maximal and/or first flow. The drop in blood pressure after restoration of arterial inflow is greater and more prolonged in patients than in normals (79.82). Several authors (79.84.89.91) found good correlations between post-ischemic blood pressures and the extent and/or localization of arterial obstructive disease.

During PIRH, one can also measure blood flow velocity and pulse volume changes.

Støren (92) investigated PIRH and calf volume changes with a mercury strain gauge plethysmograph. He found good reproducibility and stated that the method was easier to perform than blood flow measurements and just as informative.

Fronek et al (93), Simonson et al (94) and Bernink (3) combined PIRH with pulse-volume measurements of the toes. They found the toe pulse reappearance time to be a reliable and informative parameter. Fronek et al (95) and Myhre (90) combined PIRH with Doppler derived blood flow velocity measurements. Fronek et al measured flow velocity in the common femoral artery, Myhre in the posterior tibial artery. The flow velocity measurements were found to be reproducible and separated normals from those with obstructive disease.

Myhre (90) found that solitary lesions in the aorto-iliac segment produced flow velocity signals that were difficult to differentiate from normal signals.

IV.4. Pharmacological Reactive Hyperemia (PRH)

IV.4.1 Genesis of PRH

Any pharmacological agent that causes peripheral vasodilatation without undesirable side effects can, in theory, be used to increase blood flow in the extremities by intra-arterial injection.
Bardach (96) and Udoff et al (97) used tolazoline to induce vasodilatation in the evaluation of arterial disease. Tolazoline, an alpha-adrenergic competitive blocker which produces histamine like peripheral vasodilatation, causes an increase in peripheral blood flow primarily by a direct action on vascular smooth muscle (96.97). This pharmacon has not found wide acceptance.
Papaverine, a pure muscle relaxant with no alpha adrenergic blocking effects (97), was introduced by Sako (98) and is more often used to study peripheral arterial disease (99-105).

IV.4.2 The influence of papaverine on blood flow and -pressure in normal extremities and those with arterial obstructive disease.

Papaverine induces systemic vasodilatation with a resultant decrease in systemic blood pressure (103). Brachial artery pressures must be taken to monitor this decrease.
Sako (98) used 15 mg papaverine intra-arterially and found 2 to 4 fold increase in blood flow. Quin et al (99) performed a dose response study for papaverine. They concluded that papaverine was a safe, stable and non-specific vasodilatator, quickly metabolised and relatively free of systemic effects. They recommended 20 mg as the optimal dose. Williams and Flanigan (106) found that a dose of 0.5 mg/kg provides vasodilatation in both canine and human dose response studies.
Dedichen and Myhre (104) observed an increase of blood flow following papaverine injection at 88% of the maximal flow response during PIRH (occlusion time: 5 minutes) in normal individuals. In patients with arterial obstructive disease, the maximal blood flow following papaverine was significantly lower than in the normal group and amounted to 261% of the basal level (104). One can therefore expect the same pressure/flow patterns after papaverine injection as were described for PERH and PIRH (chapter IV.2.3 and IV.3.3).

1. Barcroft H., Miller J.L.E.
The blood flow through muscle during sustained contraction.
J. Physiol. 1939; 97: 17

2. Barcroft H., Dornhorst A.C.
The blood flow through the human calf during rhythmic exercise.
J. Physiol. 1949; 109: 402

3. Bernink P.J.L.M.
Parameters van de circulatie in de onderste extremiteiten met betrekking tot atherosclerosis obliterans.
Thesis, Groningen 1978

4. Haddy F.J., Scott J.B.
Metabolic factors in peripheral circulatory regulation.
Federation Proceedings 1975; 34: 2006-2011

5. Haddy F.J., Scott J.B.
Metabolically linked vasoactive chemicals in local regulation of blood flow.
Physiol. Rev. 1968; 48: 638

6. Haddy F.J., Scott J.B.
Bioassay and other evidence for participation of chemical factors in local regulation of blood flow.
Circ. Res. (suppl.1) 1971 28 and 29: 1-86

7. Bayliss W.M.
On the local reactions of the arterial wall to changes of internal pressure.
J. Physiol. 1902; 28: 220-231

8. Wahren J., Cronestrand R., Juhlin-Dannfelt A.
Leg blood flow during exercise in patients with occlusion of the iliac artery: pre- and postoperative studies.
Scand. J. Clin. Lab. Invest. 1973; 32: 257

9. Hylkema B.S.
Tussen polspalpatie en aortografie.
Diagnostische betekenis van enkele onbloedige meetmethoden by ontoereikende bloedvoorziening van de benen.
Thesis, Groningen 1975

10. Myhre H.O.
Ankle systolic blood pressure in lower limb arteriosclerosis measured by an ultrasound flow detector.
Scand. J. Clin. Lab. Invest. 1973; 31: 128-129

11. Snell E.S., Eastcott H.H.G., Hamilton M.
Circulation in lower limb before and after reconstruction of obstructed main artery.
Lancet 1960; I: 242

12. Strandness D.E., c.s.

13. Yao J.S.T., c.s.

14. Buth J.
Het vasculaire laboratorium
Thesis, Amsterdam 1978

15. Yao S.T., Needham T.N., Gourmoos C., Irvine W.T.
A comparative study of strain-gauge plethysmography and Doppler ultrasound in the assessment of occlusive arterial disease of the lower extremities.
Surgery 1972; 71: 4

16. Bollinger A., Schlumpf M., Butti P., Grüntzig A.
Measurement of systolic ankle blood pressure with Doppler ultrasound at rest and after exercise in patients with leg artery occlusions.
Scand. J. Clin. Lab. Invest. 1973; 31 suppl. 128: 123-128

17. Lorentsen E.
Calf blood pressure measurements.
Scand. J. Clin. Lab. Invest. 1973; 31: 69

18. Clyne C.A.C., Tripolitis A., Jamieson C.W. et al
The reproducibility of the treadmill walking test for claudication.
Surg. Gynecol. Obstet. 1979; 149: 727

19. Hillestad L.K.
The peripheral blood flow in intermittent claudication. IV The significance of the claudication distance.
Acta. Med. Scand. 1963; 173: 467

20. Peterson F.B.
The effect of varying walking speeds when measuring the claudication distance on horizontal and sloping levels.
Acta. Chir. Scand. 1967; 133: 627

21. Lassen N.A., Kampp M.
Calf muscle blood flow during walking studied by the Xe 133 method in normals and in patients with intermittent claudication.
Scand. J. Clin. Lab. Invest. 1965; 17: 447

22. Pentecost B.L.
The effect of exercise on the external iliac vein blood flow and local oxygen consumption in normal subjects, and in those with occlusive arterial disease.
Clin. Sci. 1964; 27: 437

23. Cobb L.A., Smith P.H., Lwai S., Short F.A.
External iliac vein flow; its response to exercise and relation to lactate production.
J. Appl. Physiol. 1969; 26: 606

24. Folse J.R.
Application of the sudden injection dye dilution principle to the study of the femoral circulation.
Surg. Gynecol. Obstet. 1965; 120: 1194

25. Reagan T.R., Miller C.W., Strandness D.E. Jr
Transcutaneous measurement of femoral artery flow.
J. Surg. Res. 1971; 11: 477

26. The peripheral blood flow in intermittent claudication. V
Plethysmographic studies. The significance of the calf blood flow at rest and in response to timed arrest of the circulation.
Acta. Med. Scand. 1963b; 174: 23

27. Rutherford R.B.
Vascular Surgery.
W.B. Saunders Co. Philadelphia 1977

28. Sumner D.S., Strandness D.E.
The relationship between calf blood flow and ankle blood pressure in patients with intermittent claudication.
Surgery 1969; 65: 763-771

29. Yao S.T.
Hemodynamic studies in peripheral arterial disease.
Br. J. Surg. 1970; 57: 761-766

30. Gay P., Roberts V.C.
Characterisation of post-exercise pressure response curves in the pedal arteries of patients with peripheral vascular disease.
J. Biomed. Eng. 1979; 1: 12-16

31. Bruyninckx C.M.A.
Pre- and postoperative evaluatie van claudicatio intermittens met behulp van een Doppler-flowmeter.
Thesis, Nijmegen 1976

32. Barendsen G.J.
Blood flow in human extremities at rest, after arterial occlusion and after exercise.
Thesis, Groningen 1973

33. Kitslaar P.J.E.H.M.
Doppler ultrasound tests in the diagnosis of chronic aorto-iliac obstruction.
Thesis, Maastricht 1982

34. Cohnheim J.
Untersuchungen über die embolische Processe.
A. Huschwald, Berlin 1872

35. Lister Lord

De l'influence de la position des membres sur la circulation.
Bull. Acad. Méd. 1878: s2, 8, 640-643

36. Roy C.S., Brown J.G.
The blood pressure and its variations in the arterioles, capillaries and smaller veins.
J. Physiol. 1879; 2: 323-359

37. Gaskell W.H.
On the tonicity on the heart and blood vessels.
J. Physiol. 1880; 3: 48-75

38. Bier A.
Die Entstehung des Collateralkreislaufs. I Der arterielle Collateralkreislauf.
Virchows. Arch. Path. Anat. 1897; 147: 256-293; 444-478

39. Rodbard S., Takeda Y., Takacs L.
Post-occlusion "hyperemia": A study on a model.
Quart J. exp. Physiol. 1969; 54: 346-365

40. Abramson D.I.
Anoxia in vascular responses in the extremities of man in health and disease.
University of Chicago Press. Chicago 1944; 126-141

41. Bayliss W.M.
The vasomotor system
Longmans, Green and Co. London 1923

42. Wachholder K.
Haben die rhythmischen Spontankontraktionen der Gefässe einen nachweisbaren Einfluss auf den Blutstrom?
Plügers Arch. Ges. Physiol. 1921; 190: 222-229

43. Klemensiewicz R.
Verfahren zur Ermittelung des Einflusses der Schwerkraft auf den Blutstrom und die Gefässe.
Handbuch der biologischen arbeidsmethoden.
Abt. v. Teil 4, 1.E. Abderhalden, Wien, 1923, 32-40

44. Folkow B.
Intravascular pressure as a factor regulating the tone of the small vessels.
Acta. Physiol. Scand. 1949; 17: 289-310

45. Folkow B.
Transmural pressure and vascular tone. Some aspects of an old controversy.
Arch. Int. Pharmacodyn. 1962; 139: 455-469

46. Patterson G.C.

The role of intravascular pressure in the causation of reactive hyperemia in the human forearm.
Clin. Sci. 1956; 15: 17-25

47. Myhre H.O.
Reactive hyperemia in the hind limbs of rabbits III The effect of hypervolemia and venous congestion.
Acta. Chir. Scand. 1975; 141: 609-614

48. Lewis T., Grant R.
Observations upon reactive hyperemia in man.
Heart 1925; 12: 73-120

49. Blair D.A., Glover W.F., Roddie J.C.
The abolition of reactive and post-exercise hyperemia in the forearm by temporary restriction of arterial inflow.
J. Physiol. 1959; 148: 648-658

50. Gentry R.M., Johnson D.C.
Reactive hyperemia in arterioles and capillaires of frog skeletal muscle following micro-occlusion.
Circulat. Res. 1972; 31: 953-965

51. Abramson D.I., Katzenstein K.H., Ferris Jr E.B.
Observation on reactive hyperemia in various portions of the extremities.
Amer. Heart J. 1941; 22: 329-341

52. Freeman N.E.
The effect of the temperature on the rate of blood flow in the normal and in the sympathectomized hand.
Amer. J. Physiol. 1935; 113: 384-398

53. Anrep von G.
On the part played by the suprarenals in the normal vascular reactions of the body.
J. Physiol. 1912; 45: 307-317

54. Freeburg B.R., Hyman C.
Blood-born vasodilating agent from ischemic tissues.
J. Appl. Physiol. 1960; 15: 1041-1045

55. Abrams M.E., Barker D.J.P., Butterfield W.J.H.
The effect of reserpine, noradrenaline and adrenaline on reactive hyperemia in the human forearm.
Clin. Sci. 1965; 29: 565-574

56. Lewis T.
The blood vessels of the human skin and their responses.
Shaw and Sons, London 1927

57. Barsoum G.S., Smirk F.H.

Observations on the increase in the concentration of a histamine-like substance in human venous blood during a period of reactive hyperemia.
Clin. Sci. 1936; 2: 353-355

58. Kwiatkowski H.
Observations on the relation of histamine to reactive hyperemia.
J. Physiol. 1941; 100: 147-158

59. Emmelin K., Emmelin N.
Histamine and reactive hyperemia
Acta. Physiol. Scand. 1947; 14: 16-18

60. Landowne M., Thompson Jr W.S.
Failure of antihistaminic drugs to reduce reactive hyperemia in man.
Proc. Soc. Exp. Biol. 1948; 69: 537-542

61. Duff F., Patterson G.C., Whelan R.F.
The effect of intra-arterial antihistamines on the hyperemia following temporary arrest of the circulation in the human forearm.
Clin. Sci. 1955; 14: 267-273

62. Folkow B., Haeger K., Kahlson G.
Observations on reactive hyperemia as related to histamine, on drugs antagonizing vasodilation induced by histamine and on vasodilator properties of adenosine-triphosphate.
Acta. Physiol. Scand. 1948; 15: 264-278

63. Stoner H.B., Green H.N.
Experimental limb ischaemia in man with especial reference to the role of adenosine-triphosphate.
Clin. Sci. 1945; 5: 159-175

64. Burch G.E., DePasquale N.P.
Bradykinin, digital blood flow, and the arteriovenous anastomoses.
Circulat. Res. 1962; 10: 105-115

65. Dornhorst A.C.
Hyperemia induced by exercise and ischaemia.
Brit. Med. Bull. 1963; 19: 137-140

66. Yonce L.R., Hamilton W.F.
Oxygen consumption in skeletal muscle during reactive hyperemia.
Amer. J. Physiol. 1959; 197: 190-192

67. Crawford D.G., Fairchild H.M., Guyton A.C.
Oxygen lack as a possible cause of reactive hyperemia.
Amer. J. Physiol. 1947; 197: 613-616

68. Guyton A.C., Ross J.M., Carrier Jr O., Walker J.R.
Evidence for tissue oxygen demand as the major factor causing autoregulation.
Circulat. Res. 1964; 15: suppl. I: 60-69

69. Bird A.D., Telfer A.B.M.
The effect of oxygen at 2 atmospheres on reactive hyperemia in the human forearm.
Surg. Gynec. Obstet. 1967; 124: 833-836

70. Schretzenmayer A.
Ueber kreislaufregulatorische Vorgänge an den grossen Arterien bei der Muskelarbeit.
Plüger Arch. Ges. Physiol. 1933; 232: 743-748

71. Fleisch A.
Les réflexes nutritifs ascendants producteurs de dilatations artérielle
Arch. Int. Physiol. 1935; 41: 141-167

72. Malméjac J., Capel A.
Intervention de réflexes locaux dans la genèse de l'hypotension qui suit la dèsocclusion de l'aorte.
C.R. Soc. Biol. 1936; 122: 958-961

73. Golenhofen K., Hildebrandt G.
Die Reaktion der menschlichen Muskelgefässe auf Durchblutungsdrosselung.
Plügers Arch. Ges. Physiol. 1957; 264: 492-512

74. Myhre H.O.
Reactive hyperemia in the hind limbs of rabbits I The effect of changes in occlusion time.
Acta. Chir. Scand. 1975; 141: 259-265

75. Patterson G.C., Whelan R.F.
Reactive hyperemia in the human forearm.
Clin. Sci. 1955; 14: 197-211

76. Eichna L.W., Wilkins R.W.
Blood flow to the forearm and calf. II Reactive hyperemia: factors influencing the blood flow during the vasodilatation following ischemia.
Bull. Johns Hopk. Hosp. 1941; 68: 450-467

77. Wilkins R.W., Eichna L.W.
Blood flow to the forearm and calf. III The effect of changes in arterial pressure on the blood flow to limbs under controlled vasodilatation in normal and hypertensive subjects.
Bull. Johns Hopk. Hosp. 1941; 68: 477-511

78. Myhre H.O.
Reactive hyperemia in the hind limbs of rabbits. II The effect of changes in oxygen tension and temperature.
Acta. Chir. Scand. 1975; 141: 265-271

79. Mahler F., Brunner H.H., Fronek A., Bollinger A.

Der Knöchelarteriendruk während reaktiver Hyperämia bei Gefässgesunden und Patienten mit arteriellen Verschlusskrankheit.
Schweiz. Med. Wschr. 1975; 105: 1786-1788

80. Siggaard-Andersen J.
Obliterative vascular disease. Classification by means of the Dohn plethysmograph.
Acta. Chir. Scand. 1965; 130: 190-198

81. Ehringer H.
Die reaktive Hyperämie nach arterieller Sperre.
In: Messmethoden bei arteriellen Durchblutungsstörungen.
Bollinger und U. Brunner, Bern und Stuttgart 1971; 20-33

82. Delius W.
Hämodynamische Untersuchungen über den systolischen Blutdruck und die arterielle Durchblutung distal von arteriellen Gefässverschlüssen an den Extremitäten.
Z. Kreisl.-Forsch. 1969; 58: 319-332

83. Keagy B.A., Pharr W.F., Thomas D., Bowes D.E.
Comparison of reactive hyperemia and treadmilltest in the evaluation of peripheral vascular disease.
Am. J. Surg. 1981; 142: 158-161

84. Johnson W.C.
Doppler ankle pressure and reactive hyperemia in the diagnosis of arterial insufficiency.
J. Surg. Res. 1975; 18: 177-180

85. Hummel B.W., Hummel B.A., Mowbry A. et al
Reactive hyperemia vs treadmill exercise testing in arterial disease.
Arch. Surg. 1978; 113: 95-98

86. Baker J.D.
Poststress Doppler ankle pressure: A comparison of treadmill exercise with 2 methods of induced hyperemia.
Arch. Surg. 1978; 113: 1171-1173

87. Dahn J.
On clinical use of venous occlusion plethysmography of calf. II Results in patients with arterial disease.
Acta. Chir. Scand. 1965; 130: 61-75

88. Bollinger A., Mahler F., Zehender O.
Kombinierte Druck- und Durchflussmessungen in der Beurteilung arterieller Durchblutungsstörungen.
Dtsch. Med. Wschr. 1970; 95: 1039-1043

89. Bienmuller H.
Frühdiagnostik oblitierender Gefässerkrankungen der unteren Gliedmasen. Wertigkeit verschiedener unblutiger apparativer

Untersuchungsverfahren.
Med. Klin. 1975; 70: 1139-1147

90. Myhre H.O.
Reactive hyperemia of the human lower limb. Measurement of postischaemic blood flow velocity in controls and in patients with lower limb atherosclerosis.
VASA 1975; 4: 145-149

91. Van de Water J.M., Indech C.D.V., Indech R.B., Randall H.
Hyperemic response for accurate diagnosis of arterial insufficiency.
Arch. Surg. 1980; 115: 851-856

92. Støren G.
Calf volume changes during postischemic hyperemia in normal and arteriosclerotic legs.
Scand. J. Clin. Lab. Invest. 1967; 20: 147-156

93. Fronek A., Coel M., Bernstein E.F.
Post-occlusive reactive hyperemia and the toe pulse reappearance time in the evaluation of arterial disease. In: Non-invasive diagnostic techniques in vascular disease.
C.V. Mosby Company, St. Louis 1978; 322-329

94. Simonson E., Koff S., Keys A., Minckler J.
Contour of the toe pulse, reactive hyperemia, and pulse transmission velocity; group and repeat variability, effect of age, exercise and disease.
Am. Heart J. 1955; 50: 260-279

95. Fronek A., Johansen K., Dilley R.B., Bernstein E.F.
Ultrasonographically monitored post-occlusive reactive hyperemia in the diagnosis of peripheral arterial occlusive disease.
Circulation 1973; 48: 149-152

96. Bardach G.
Eine neue methode zur direktmessung des aortofemoralen Druckgradienten in Rahmen der translumbalen Aortographie.
Fortschr Röntgenstr. 1978; 128: 317-318

97. Udoff E.J., Klemens H., Barth et al
Hemodynamic significance of iliac artery stenosis. Pressure measurements during angiography.
Radiology 1979; 132: 289-293

98. Sako Y.
Papavarine test in peripheral arterial disease.
Surgical Forum 1966; 17: 141-143

99. Quin R.O., Evans D.H., Bell P.R.F.
Hemodynamic assessment of the aorto-iliac segment.
J. Cardiovas. Surg. 1975; 16: 586-589

100. Barber G.G. et al
Hemodynamic assessment of the aorto-iliac segment: A prospective study.
Can. J. Surg. 1980; 23: 542-544

101. Baron H.C., Schwartz M., Batri G.
The papaverine test for blood flow potential of the profunda femoris artery.
Surg. Gynecol. Obstet. 1981; 153: 873-876

102. Archie Jr J.P., Feldtman R.W.
Intraoperative assessment of the hemodynamic significance of iliac and profunda femoris artery stenosis.
Surgery 1981; 90: 876-880

103. Flanigan D.P., Williams L.R., Schwartz J.A. et al
Hemodynamic evaluation of the aorto-iliac system based on pharmacologic vasodilatation.
Surgery 1983; 93: 709-714

104. Dedichen H., Myhre H.O.
Reactive hyperemia of the human lower limb.
Acta. Chir. Scand. 1975; 141: 517-521

105. Castaneda-Zuniga W., Knight L., Formanek A. et al
Hemodynamic assessment of obstructive aorto-iliac disease.
Am. J. Roentgenol. 1976; 127: 559-561

106. Williams L.R., Flanigan D.P.
Detection of subcritical iliac artery stenoses with pharmacologic vasodilatation.
Surg. Forum 1982; 33: 451-453

CHAPTER V

DE REACTIEVE-HYPEREMIEPROEF; EENVOUDIG UITVOERBARE METHODE OM DE PERIFERE, ARTERIELE, BLOEDSTROOM ONDER BELASTING TE ONDERZOEKEN.
(THE REACTIVE HYPEREMIATEST, A SIMPLE METHOD TO TEST THE PERIPHERAL, ARTERIAL CIRCULATION DURING EFFORT.)

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V.1. Introduction

The purpose of reconstructive vascular surgery is to optimize arterial blood flow.
It is not always easy to select the right reconstructive procedure for a certain patient.
Factors, important in clinical decision making are: the severity of the atherosclerotic disease, the way the disease influences the patients daily life, the risk of the operation and long-term results of the vascular reconstruction. Although history and physical examination are very important in clinical decision making, their interpretation remains subjective (1).
Angiography is an invasive method, with its specific complications and it provides only anatomical and no functional information (2).
On top of that, angiography gives no information about the visco-elastic properties and origins of turbulence in a blood vessel. The above mentioned factors may be of little influence at rest, but, during higher blood-flow velocities, they may become very important (3.4.5).
A need for objective methods to measure the function of the arterial circulation in patients with peripheral arterial occlusive disease therefore exists (1).
The treadmill test, combined with the measurement of the systolic ankle blood pressure, is frequently used to stress and test the peripheral arterial circulation (6).
This test is rather elaborate and not every patient is able to perform the test.
The reactive hyperemia test is easier to perform and might very well be just as useful as the treadmill-test. Therefore it seemed interesting to compare the two methods.

Patients and methods

The group under study consisted of 30 persons, one randomly selected extremity per person was used. Twenty men and four women, aged 37 to 71 years, had intermittent claudication, and two men and four women, aged 21 to 48 years, were healthy controls. All persons underwent both tests (the treadmill test and the reactive hyperemia test).

The reactive hyperemiatest

After the patient has been in a supine position for half an hour at room temperature, a blood pressure cuff is placed just above the ankles, while the patient is still in the supine position.
The systolic blood pressure in the dorsal pedal artery and posterior tibial artery are measured using Doppler-ultrasound.
In both upper extremities the blood pressure is measured in the conventional way.
With the data, the ankle-arm pressure index at rest is calculated. The index for healthy controls is 100% or more (7).
The next step is to place a tourniquet of 75 x 9 cm around the thigh and to empty the venous system by elevating the extremity.

During elevation the tourniquet is inflated until the arterial pulsations at the ankle are no longer detectable with Doppler-ultrasound. We prefer not to raise the pressure in the tourniquet above 300 mm of mercury.
The tourniquet occlusion is maintained for four minutes (8.9).
After deflating the tourniquet, a clearly visible hyperemia appears below the tourniquet.
During the following two minutes, the systolic blood pressure at the ankle is measured every fifteenth second.
The ankle-arm blood pressure indices are calculated and a curve is made. (Fig. 1)

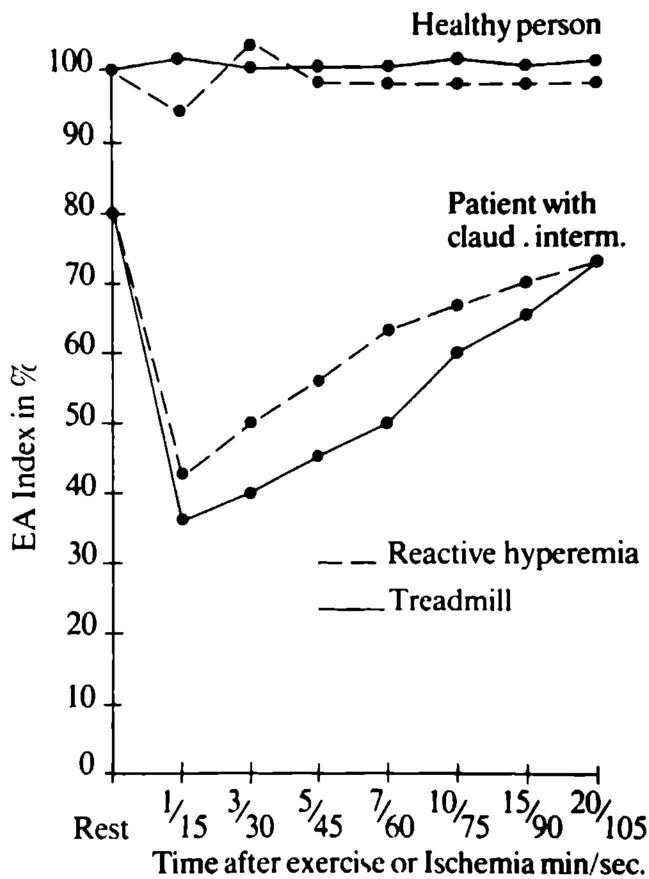

Figure 1. Representative curves of the ankle-arm blood pressure indices (EA-index) in percents, of a healthy person and of a claudicant during reactive hyperemia and after exercise.

The same procedure is then performed on the other extremity.
The curve is given its characteristic shape by the index at rest, the lowest index during reactive hyperemia and the time it takes for the blood pressure index to return to the level at rest (Index recovery time).

The treadmill test

Under the same conditions as mentioned with the reactive hyperemia test, the ankle-arm pressure index at rest is determined. The patient then walks on a treadmill with an inclination of 12^{o} at a speed of 3 kilometres an hour, for five minutes or until ischemic pain forces him to stop.
Immediately after exercise the patient resumes the supine position and blood pressure cuffs are placed around the ankles and arms.
After 1, 3, 5, 7, 10, 15 and 20 minutes the blood pressures are determined at both ankles with Doppler-ultrasound.
The ankle-arm blood pressure index is calculated using a simultaneously measured arm blood pressure and a curve is made (Fig. 1). The curve is again given its characteristic shape by the index at rest, the lowest index after exercise and index recovery time.

Statistical analysis

To compare the methods, the linear correlation of the lowest indices and the index recovery times of both tests was calculated for 30, randomly selected extremities.

Results

After acquiring some experience, the performance of the reactive hyperemia test was a simple procedure. The tourniquet occlusion was well tolerated by the patients.
It took about 15 minutes to perform a test, the performance of a treadmill-test took about 30 to 45 minutes.
In the group of patients with intermittent claudication, the ankle-arm index decreased from an index at rest of 65.7% (normally 100% or more) to a lowest index of 31.7% during reactive hyperemia, compared with 34.7% after treadmill exercise.
The systolic ankle blood pressure did not decrease, sometimes it even increased, after exercise in the healthy control group.
During reactive hyperemia, on the other hand, the ankle blood pressure usually showed a slight decrease. Like Johnson (10), we found that the index recovery time was less than 30 seconds. In the group with intermittent claudication the index recovery time after exercise was more than 5 minutes in 93%. This is comparable with the fact that in the same group, the index recovery time was more than 45 seconds in 90%, during reactive hyperemia. (Fig. 1)
A good correlation existed between the lowest indices of both tests ($r = 0.94$, $p < 0.00001$) (Fig. 2); the correlation between the recovery times was reasonable ($r = 0.77$, $p < 0.00001$).

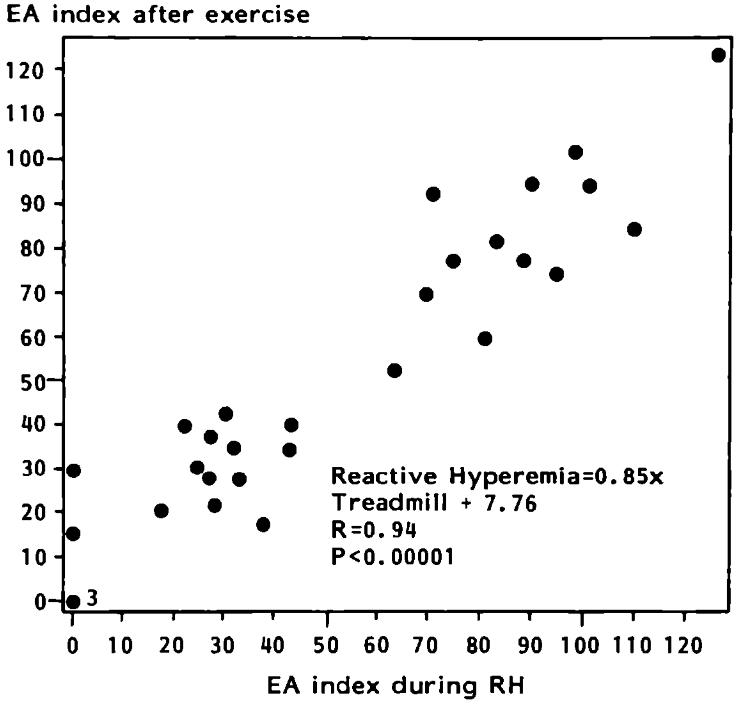

Figure 2: Linear correlation between the minimum ankle-arm blood pressure indices (EA-index) during post-ischemic Reactive Hyperemia (RH) and after treadmill-exercise of 24 claudicants and 6 healthy controls.

Discussion

When a healthy person starts to walk, the peripheral arterial resistance decreases, followed by an increase in blood flow velocity in the major arterial vessels.

Through this mechanism the peripheral blood pressure is maintained at a constant level.
In patients with obstructive vascular disease there is a loss of energy in stenotic areas and collateral vessels, causing a lowered peripheral blood pressure at rest. Because the loss of energy is a function of blood flow velocity (11), the energy-loss increases during higher blood flow velocities. The result is a drop in peripheral systolic blood pressure.
The more extensive the atherosclerotic lesions are in the femoro-popliteal and aorto-iliac segments, the more severe the decrease in systolic ankle blood pressure will be after exercise (7).
A decrease in peripheral arterial resistance can also be evoked by means of reflex vasodilatation; for instance during reactive hyperemia after a period of ischemia (1,8).
Post-Ischemic Reactive Hyperemia as a method of assessing the severity of obstructive atherosclerotic disease has been mentioned before in the literature.
Nieveen et.al. (12) identified the hyperemic effect with the naked eye. In later studies, plethysmographic methods were used to measure the blood flow during reactive hyperemia (13,14).
Easier than measuring blood flow is the determination of the blood pressure at the ankle (10.15.16) especially since Doppler-ultrasound has made this a very reliable and easy procedure.
Measurement of the blood pressure at rest and after exercise has therefore become a standard procedure in many surgical clinics.
Because both exercise and ischemia cause vasodilatation and therefore similar changes in peripheral arterial blood pressure, it was logical to compare both methods.
Hummel et al (17) and Baker (18) found, like we did, an excellent correlation between both tests, especially regarding the maximal blood pressure response.
They, too, found that the correlation between the recovery times was poorer because of the basic differences between both tests, and because the treadmill test data are dependent upon a very subjective criterion, namely ischemic pain.
The reactive hyperemia test however is not patient-dependent and therefore standardized. This standardization is the greatest advantage of the reactive hyperemia test.
Other advantages of the test are that it takes less time and space to perform. The reactive hyperemia test can also be performed on patients who cannot walk because of tissue loss, amputation, or who are disabled by cardio-pulmonary diseases in which case, the treadmill test can be dangerous. The reactive hyperemia test gives better information about the hemodynamic condition of the other, asymptomatic extremity of the patient. When the patient stops walking on the treadmill because of ischemic pain in one extremity, the other extremity may be submaximally stressed. Even in the immediate post-operative phase, the test can be performed to check the result of a vascular reconstruction.
Only the presence of a femoro-popliteal bypass is possibly a contra-indication to the test.
We have no data however indicating that inflation of a

thigh-tourniquet can cause thrombotic occlusion of a femoro-popliteal bypass.
The treadmill test has the advantage that the walking time and distance can be measured.
Further investigations with the reactive hyperemia test will need to determine whether or not the test is able to help us in the localization of the hemodynamically important lesions.
Based on our own results and those of others we can conclude that in the diagnosis of obstructive atherosclerotic disease, the reactive hyperemia test can replace the treadmill test. The reactive hyperemia test seems to be preferable because it is easier for the patient and the examiner.

V.2. ADDENDUM

In this addendum more attention will be paid to the findings of other authors concerning the relation of the PIRH test to the PERH test.
In chapter V only Hummel et al (17) and Baker (18) were mentioned , who both found a good correlation between the PIRH and the PERH test.
In his comparative study, Hillestad (19) stated that the PIRH test is preferable to a PERH test if the blood supply to the lower extremities has to be assessed.
Dahn (20) stated that exercise during arterial occlusion as a test appears inferior to a PIRH test, when the aim of the study is to distinguish between patients with arterial obstructive disease and healthy persons.
Ehringer (21) compared a PIRH test to an ergometertest. He found that the ergometer test caused more hyperemia but stated that the PIRH test is a good indicator of the degree of collateral circulation. He preferred the PIRH test also because the reproducibility was better.
Mahler et al (22) found a good correlation between the PIRH test and the PERH test in healthy persons and athletes. The maximal blood flow responses correlated particularly well.
They refer to authors who state that in healthy persons the systolic blood pressure shows a short drop directly after exercise as can be observed directly after ischemia.
Bartoli and Dorigo (23) found a good correlation in healthy persons, and a poorer correlation in patients, between the PIRH- and PERH tests. The PIRH curve in the patients, however, showed a clearly recognizable, pathological pattern.
Fox et al (24) found a good correlation between maximal blood pressure response in both tests. They concluded that the PERH test was preferable.
Berni nk (25) concluded that the maximal blood flow after strenuous exercise could be considerably more than post-ischemic blood flow. He stated that both PERH and PIRH provide a good assessment of the arterial capacity of the legs.
Ouriel et al (26) compared a treadmill test, a PIRH test and resting ankle pressure measurements in 218 patients and 25 healthy persons. They studied the diagnostic accuracy and reproducibility of the three methods.
The ankle pressure index at rest proved to be the most reproducible parameter.
In differentiating between diseased and normal limbs, as defined angiographically, the resting index and the treadmilltest were more valuable than the PIRH test.
It is however important to mention that the tourniquet used in their PIRH test was positioned below the knee.
The reactive hyperemia therefore was probably less than that obtained from a test with a tourniquet in the above-knee position.
Keagy et al (27) found a large maximal drop in blood pressure in healthy persons during PIRH. The drop was 34% $\pm$ 7%, which is impressive when compared to results of others (Johnson (10): 23% $\pm$ 12%, Hummel et al (17) 17% $\pm$ 11%, Baker (18) 17%). Although the correlation of the maximal blood pressure response in both tests was

good in the patient group, the specificity of the PIRH test suffered from the large pressure drop which occured in the healthy persons. Their findings are probably not due to occult arterial obstructive disease in their healthy group of patients, because the ages varied from twenty to thirty-five.
The conclusion must be, that, whatever practical advantages the PIRH test may have over the treadmill test, it is not correct to use simply one test instead of the other without adjusting the criteria for health and disease.

V.3. Conclusion; and introduction to the next chapters

The final conclusion of this study and review, is that the PIRH test is a simple, easy and standardized test.
The maximal blood pressure response during PIRH correlates well with the maximal response after exercise, especially in the group with arterial obstructive disease.
The return times of the blood pressure to its resting value during PIRH and PERH do not correlate as well.
For the purpose of this study the PIRH test was preferred.
In the next chapters, further investigation with the PIRH test is described, concerning its reproducibility and its value in assessing the extent and localization of arterial obstructive disease.

1. Brener B.J., Raines J.K., Darling R.C., Austen W.G.
Measurement of systolic femoral arterial pressure during reactive hyperemia; an estimate of aorto-iliac disease.
Circulation, 1974; 49-50 (Suppl. II): 259-267.

2. Strandness Jr D.E., Sumner D.S.
Non-invasive methods of studying peripheral arterial function.
J. Surg. Res., 1972; 12: 419-430.

3. Cappelen Jr, C., Hall K.V.
The effect of obstructive arterial disease on the peripheral arterial blood-pressure. Registrations from the dorsalis pedis artery of normal persons and patients before and after operation.
Surgery 1960; 48: 888

4. Schultz R.D., Hokanson D.E., Strandness Jr, D.E.
Pressure-flow and stress-strain measurements of normal and diseased aorto-iliac segments.
Surg. Gynec. Obstet, 1967; 124: 1267-1276.

5. Moore W.S., Hall A.D.
Unrecognized aorto-iliac stenosis; A physiologic approach to the diagnosis.
Arch. Surg., 1971; 103: 633-638.

6. Strandness Jr. D.E., Sumner D.S.
Applications of ultra-sound to the study of arteriosclerosis obliterans.
Angiology, 1975; 26: 187-198.

7. Yao S.T., Hobbs J.T., Irvine W.T.
Ankle systolic pressure measurements in arterial disease affecting the lower extremities.
Brit. J. Surg., 1969; 56: 676-679.

8. Barcroft H.
The mechanism of vasodilatation in the limbs during and after arrest of the circulation.
Angiology, 1972; 23: 595-599.

9. Dedichen H., Myhre H.O.
Reactive hyperemia of the human lower limb.
Acta Chir. Scand. 1975; 141: 517-521.

10. Johnson W.C.
Doppler ankle pressure and reactive hyperemia in the diagnosis of arterial insufficiency.
J. Surg. Res., 1975; 18: 177-180.

11. Keitzer W.F., Fry W.J., Kraft R.O., DeWeese M.S.
Hemodynamic mechanism for pulse changes seen in occlusive vascular disease.

Surgery, 1965; 57: 163-174.

12. Nieveen J., Rodbard J.A., van Wijk Th.W.
Onderzoek en behandeling van perifere vaatziekten. Ervaringen met cyclospasmol.
Ned. T. Geneesk., 1954; 98: 205-216.

13. Dornhorst A.C.
Hyperemia induced by exercise and ischemia.
Brit. Med. Bull, 1963; 19: 137-140.

14. Hillestad L.K.
The peripheral blood flow in intermittent claudication.
Acta Med. Scand., 1963; 174: 671-685.

15. Delius W.
Hämodynamische Untersuchungen über den systolischen Blutdruck und die arterielle Durchblutung distal von arteriellen Gefässverschlüssen and den unteren Extremitäten.
Zeitschrift für Kreislaufforschung, 1969; 58: 319-333.

16. Mahler F., Brunner H.H., Fronek A., Bollinger A.
Der Knöchel arterien-druck wahrend reaktiver Hyperämie Gefässgesunden und Patienten mit arterieller Verschlusskrankheit.
Schweiz. Med. Wschr., 1975; 105: 1786-1788.

17. Hummel B.W., Hummel B.A., Mowbry A., Maixner W., Barnes R.
Reactive hyperemia vs treadmill exercise testing in arterial disease.
Arch. Surg., 1978; 113: 95-98.

18. Baker J.D.
Poststress Doppler ankle pressure: A comparison of treadmill exercise with two other methods of induced hyperemia.
Arch. Surg., 1978; 113: 1171-1173.

19. Hillestad L.K.
The peripheral blood flow in intermittent claudication no VII.
Acta Med. Scand. 1963; 174: 687-700.

20. Dahn J.
On clinical use of venous occlusion plethysmography of calf - II results of patients with arterial disease.
Acta Chir. Scand. 1965; 130: 61-75.

21. Ehringer H.
Die reaktive Hyperämie nach arterieller Sperre.
In: Aktuelle Probleme in der Angiology
ed: Bollinger A., Brunner H. 1971, Band 13: 20-33.

22. Mahler F., Koen L., Johansen K.H., Bernstein E.F., Fronek A.
Postocclusion and postexercise flow velocity and ankle pressures in normals and marathon runners.

Angiology 1976; 27: 721-729.

23. Bartoli V., Dorigo B.
Comparison between reactive and exercise hyperemia in normal subjects and patients with peripheral arterial disease.
Angiology 1979; 30: 40-47.

24. Fox M.J., Tripolitis A., Kirby S., Jamieson C.W.
A comparison of a reactive hyperaemia test with a standard exercisetest in the evaluation of peripheral vascular disease.
Brit. J. Surg. 1977; 64: 290

25. Bernink P.J.L.M.
Parameters van de circulatie in de onderste extremiteiten met betrekking tot atherosclerosis obliterans.
Thesis, Groningen, 1978.

26. Ouriel U., McDonnel A.E., Metz C.E., Zarius C.U.
A critical evaluation of stress testing in the diagnosis of peripheral vascular disease.
Surgery 1982; 91: 686-693.

27. Keagy B.A., Pharr W.F., Thomas D., Bowes D.E.
Comparison of reactive hyperemia and treadmilltests in the evaluation of peripheral vascular disease.
Am. J. Surg. 1981; 142: 158-161.

ANKLE PRESSURE CHANGES DURING REACTIVE HYPEREMIA IN PERIPHERAL ARTERIAL DISEASE.

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VASA, 1983, 12, 29-34.

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Introduction

As already indicated by Yao et al. in 1969 (23) and many others (4.13.21), measurement of the ankle blood pressure makes it possible to asses the severity of peripheral arteriosclerosis. For patients where symptoms already exist at rest (stages III and IV according to Fontaine) these data are usually sufficient. For patients with intermittent claudication (Fontaine's stage II), however, the values at rest are often considered to be insufficient indication of the severity of the symptoms during exercise.
Therefore there is a need for tests approaching reality more closely, i.e. the occurrence of symptoms and signs during exercise. Frequently the treadmill test is used, in which the response of the ankle blood-pressure is determined after exercise.
The degree of reduction of the ankle blood-pressure in relation to the pressure at rest and the time necessary for its return to the pressure at rest might yield additional information on the severity and extent of the peripheral arteriosclerotic changes (3.5.15.19.20.21).
Recently, some authors (1.11) have drawn attention to the pattern of the blood-pressure changes at the ankle measured during reactive hyperemia - after a period of induced ischaemia. This pattern shows a marked resemblance to the pressure changes after exercise.
Our experience with the reactive hyperemia test - both as regards comparison with the treadmill test and as regards assessment of the severity of the peripheral vascular changes - is described in the present publication.

Patients and methods

To permit comparison of the reactive hyperemia test and the treadmill test, both tests were performed in a group of 30 subjects (24 patients with intermittent claudication and 6 healthy subjects without vascular symptoms), with 56 extremities being examined.
Then the reproducibility of the reactive hyperemia test was assessed in 10 patients with intermittent claudication (20 extremities) by carrying out the test twice in succession.
Finally, the reactive hyperemia test was performed in 170 persons (248 extremities), classified into 4 groups according to the clinical picture:

1. no symptoms or atypical intermittent claudication (n = 69)
2. moderate intermittent claudication, walking-distance more than 100 m (n = 119)
3. serious intermittent claudication, walking-distance less than 100 m (n = 37)
4. pain at rest (n = 23).

Reactive hyperemia test

The patient is in the supine position and a blood-pressure cuff is applied to both legs just above the ankles. The systolic blood-pressure in the posterior tibial and dorsalis pedis arteries is determined by Doppler flow measurement. The blood-pressure in both arms is measured conventionally. Then a tourniquet of 75 x 9 cm is applied to one of the thighs and the venous system is emptied by passively lifting the leg. In this position of the leg the cuff is inflated until the vascular tones at the ankle cannot be heard with the Doppler probe. The pressure is than raised by another 100 mm Hg, a pressure of 300 mm Hg preferably not being exceeded. The ischaemia of the leg thus induced is maintained for 4 minutes. Then the tourniquet is rapidly deflated, after which a clearly visible hyperemia ensues in the leg.

The ankle blood-pressure is then measured every 15 seconds for 2 minutes. The results are expressed as percentages of the pressure initially measured in the arm and plotted as a curve. The shape of the curve obtained is characterized by the index at rest, the 15 sec index (deepest point of the curve) and the duration of the recovery. The same procedure is then followed for the other leg (Fig. 1).

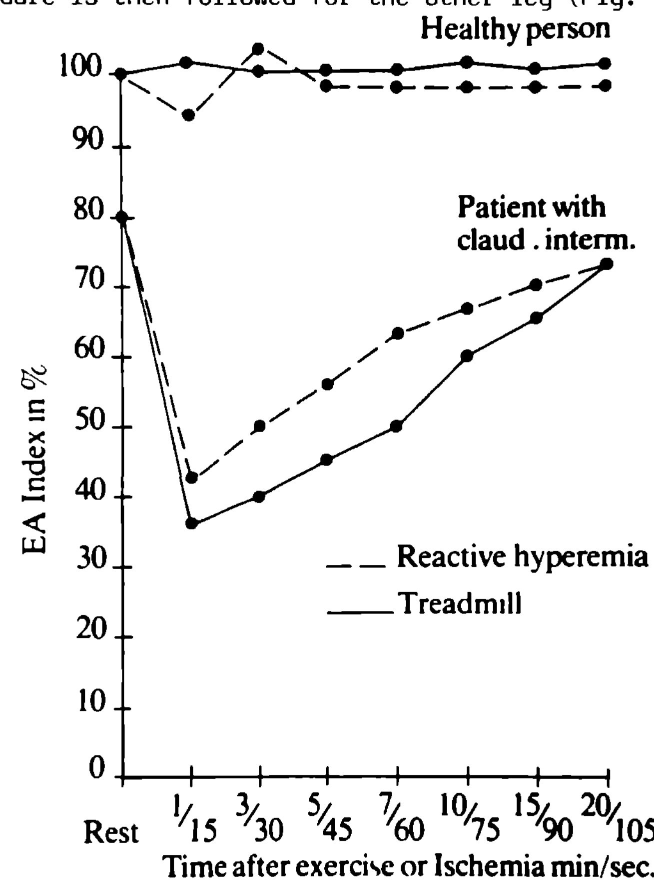

Figure 1. Representative curves of the ankle-arm blood pressure indices (EA-index) in percents, of a healthy person and of a claudicant during reactive hyperemia and after exercise.

The treadmill test

After the patient has been in supine position for half an hour the index at rest is determined. Then he walks on the treadmill, with a speed of 3 km/h and a inclination of 12^{o}, for 5 minutes or until he is forced to rest by pain in the legs. The patient then lies down on the examination table and blood-pressure cuffs are applied to the upper arms and lower legs. The blood-pressure at both ankles is measured with the Doppler probe after 1, 3, 5, 7, 10, 15 and 20 minutes or until the blood-pressure at rest has again been reached.
The results are expressed as a percentaqe of the highest simultaneously measured systolic blood-pressure in the arms and plotted as a curve which is again characterized by index at rest, 1 min index (deepest point) and recovery time (Fig. I).
In comparing the reactive hyperemia and treadmill tests all values obtained, both at rest and after ischaemia or exercise, were correlated, 15 sec hyperemia being correlated with 1 min after exercise, 30 sec hyperemia with 3 min after exercise, etc.
In studying the value of the reactive hyperemia test for assessment of the severity of symptoms the index at rest, the 15 sec index and the index gradient, i.e. the difference between the index at rest and the 15 sec index, were recorded and compared.

Data analysis

The correlation between the response of the ankle pressure index during reactive hyperemia and that following treadmill exercise was established by linear regression analysis. The paired student test was used in the reproducibility study ($p > 0.05$). The test of Kruskal and Wallis finally was used in the study where reactive hyperemia data were correlated with clinically divided groups of patients ($p < 0.10$).

Results

With some experience, the reactive hyperemia test was found to be simple in practice. Ischaemia for 4 minutes is well tolerated by the patients. The time required for the test was approximately 15 minutes in comparison with the 40 to 45 minutes required for a treadmill test.
In the group of patients with symptoms the average ankle-arm index after ischaemia fell from an initial value of 65.7% (normally 100% or higher) to 31.7%. In the same group a reduction to an ankle-arm index of 34.7% was seen after treadmill testing.
In patients without symptoms no major changes in the ankle blood-pressure were noted either during hyperemia or after exercise.
In the group of patients with intermittent claudication the time required for the ankle blood-pressure to return to its value at rest after treadmill testing exceeded 5 minutes in 93% of cases. In the same group of patients 90% of the reactive hyperemia tests showed that the ankle blood-pressure took more than 45 seconds to return to its value at rest.
As regards the paired indices found during reactive hyperemia and after exercise, a very good correlation between the two tests was

found for the entire group of tested subjects (r = 0.92 for p < 0.00001) (Fig. 2).

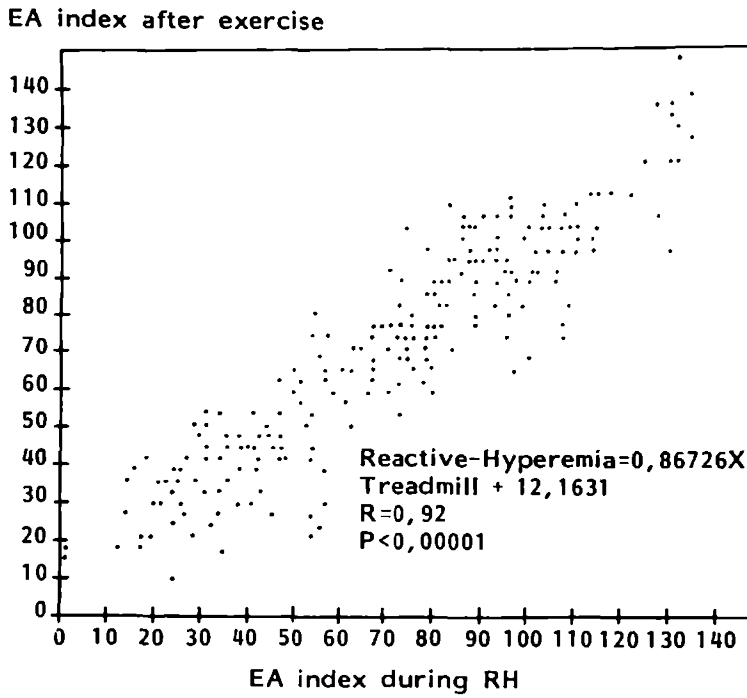

Figure 2: Linear correlation between the paired ankle-arm blood pressure indices during reactive hyperemia and after exercise.

The correlation between the minimal indices (15 sec and 1 min indices) during reactive hyperemia and after exercise was excellent also in both tests ($r = 0.91$ for $p < 0.00001$). The correlation between the two tests as regards the time required for return to the pressure at rest was less satisfactory ($r = 0.77$ for $p < 0.00001$).
Reproducibility of the reactive hyperemia test is good, because the paired values found for two successive tests were never found to differ significantly ($p > 0.05$). A difference of more than 15%, measured at two corresponding times in two successive tests, indicates the existence of a haemodynamic chance (with a 5% chance of erroneous assessment).
The values found for the index at rest, the 15 sec index and the index gradient in the four clinically different patient groups are given in Table I.

Table I: Mean values and standard deviations of resting ankle-arm pressure index (EA Index), the EA index after 15 sec Reactive hyperemia (the deepest point of the curve) and the index gradient (the difference between resting EA index and 15 sec EA index).

Group	Clinical picture	n	Mean and standard deviations			
			in rest	after 15 sec RH	of the index gradient	
A	No claudication	69	112.1 ± 11.6[1]	92.7 ± 16.3[1]	19.4 ± 14.2[1]	
B	Moderate claudication	119	72.0 ± 13.9[1]	39.4 ± 15.2[1]	32.6 ± 11.4[1]	2
C	Severe claudication	37	53.9 ± 11.8[1,2]	14.1 ± 14.5[1,2]	39.8 ± 13.3[1]	2
D	resting pain	23	50.4 ± 16.1[2]	7.9 ± 11.7[2]	42.5 ± 19.4[2]	

[1] Significantly different ($p < 0.005$) from each other.
[2] Not significantly different from each other.

This shows that by means of the index at rest alone all groups can be clearly distinguished except groups C and D. Also, all groups can be significantly distinguished by the 15 sec index except again groups C and D.
The index gradient distinguished group A from group B, group A from group C and group B from group C. No significant distinction could be made between groups B and D and groups C and D.

Discussion

In patients with arterial disease the energy loss in stenoses and collaterals will be such that the systolic blood-pressure distal to a stenosis or obstruction is reduced, even at rest. Because the energy loss is a function of the flow velocity of blood (14), this energy loss will increase when the flow velocity increases, as occurs during walking due to a fall in the peripheral resistance. Such a reduction of the peripheral resistance followed by an increase of blood-flow velocity, as seen after exercise, can also be induced by means of the reflex vasodilation which occurs after temporary ischaemia of the leg. After a period of ischaemia an extremity shows reactive hyperemia (8.10.12.16.17.18). It is not yet entirely clear how this vasodilatation occurs. There are indications that during ischaemia anoxia plays a role (9), but the vasodilatation persists after tourniquet deflation longer than can be explained by ischaemia alone (2). The explanation may be found in the effect of vasodilator metabolites.
Dedichen and Myhre (8) demonstrated that in normal extremities the blood-flow velocity after occlusion for 5 minutes is 485% of the basal velocity. The maximal blood-flow velocity increased only slightly if the occlusion lasted for more than 2 minutes.
More simple than measurement of the blood-flow velocity during reactive hyperemia (6.10) is determination of the systolic blood-pressure, which depends on the peripheral resistance and blood-flow. This is especially so since the introduction of the Doppler system has made this a simple and highly accurate technique. Because the effects of exercise on the one hand and reactive hyperemia on the other on the distal blood-pressure show such marked similarities, it was reasonable to compare the two methods in a study on patients with peripheral arteriosclerosis (10.11.12). As in our study, an excellent correlation was found between the reactive hyperemia and the treadmill tests especially as regards the maximal reduction of blood-pressure after exercise or ischaemia. Correlation was less good as regards recovery times. This may be due to the fact that it is the subjective nature of pain in intermittent claudication which determines the duration of the treadmill exercise. Therefore, this is not a standardized determination.
In contrast to the treadmill test, the reactive hyperemia test is standardized. This standardization is, in our opinion, the first and principal advantage of the reactive hyperemia test in comparison with the treadmill test. Other important advantages are that the reactive hyperemia test can also be safely used on patients with serious cardiovascular disability, and that a good impression is also gained

of the severity of the vascular condition of the asymptomatic extremity. Such data can be especially helpful in the follow-up of these patients. In addition, there are some less important advantages, e.g. the fact that the test requires little time and can be carried out in a relatively small room or even as a bedside procedure, or immediately after a vascular reconstruction. Reproducibility of the reactive hyperemia test has been found to be good, another advantage over the treadmill test, whose reproducibility is doubtful (7).

The results of our study show that, in the reactive hyperemia test especially, the 15 sec index and the index gradient do not yield more information as regards assessment of the severity of the peripheral vascular disease than the index at rest alone. In this context the reactive hyperemia test does not therefore improve our diagnostic armamentarium.

However, some of our preliminary results indicate that these supplementary data may play a part in the non-invasive determination of the localization of haemodynamically important changes, as was also found by other authors (17.22). Further studies in this direction are therefore indicated.

1. Baker J.D.
Poststress Doppler ankle pressure.
Arch. Surg. 1978; 113: 1171.

2. Barcroft H.
The mechanism of vasodilatation in the limbs during and after arrest of the circulation.
Angiology 1972; 23: 595.

3. Bollinger A.
Laufbandergometrie und Muskelfunktion bei Claudicatio intermittens.
Schweiz. Med. Wochenschr. 1973; 103: 636.

4. Carter S.A.
Clinical measurement of systolic pressures in limbs with arterial occlusive disease.
JAMA 1969; 207: 1869

5. Carter S.A.
Response of ankle systolic pressure to leg exercise in mild or questionable arterial disease.
N. Eng. J. Med. 1972; 287: 578.

6. Clement D.L., Charlier P., de Meunynck C.
Diagnostic performance of ECG triggered venous occlusion plethysmography.
In: Dietrich E.G. (Ed.): Non-invasive Cardiovascular Diagnosis, second edition, 1981.

7.Clyne C.A.C., Tripolitis A., Jamieson C.W., Gustave R., Stuart Fr.
The reproducibility of the treadmill walking test for claudication
Surg. Gynecol. Obstet 1979; 149: 727.

8. Dedichen H., Myhre H.O.
Reactive hyperemia of the human lower limb. A comparison between the effect of tourniquet occlusion, selective arterial occlusion and intra-arterial papaverine injection.
Acta Chir. Scand. 1975; 141: 517.

9. Fairchild H.M., Ross J., Guyton A.C.
Failure of recovery from reactive hyperemia in the absence of oxygen.
Am. J. Physiol. 1966; 210: 490.

10. Hillestad L.K.
The peripheral blood-flow in intermittent claudication, VI plethysmographic studies. The blood-flow response to exercise with arrested and with free circulation.
Acta Med. Scand. 1963; 174: 671.

11. Hummel B.W., Hummel B.A., Mowbry A., Maixmer W., Barnes R.W.
Reactive hyperemia vs treadmill exercise testing in arterial disease.
Arch. Surg. 1978; 113: 95.

12. Johnson W.C.
Doppler ankle pressure and reactive hyperemia in the diagnosis of arterial insufficiency.
J. Surg. Res. 1975; 18: 177.

13. Johnston K.W.
Systolic slope and other pressure measurements in patients with peripheral vascular disease.
Surg. Gynecol. Obstet. 1975; 140: 249.

14. Keitzer W.F., Fry W.J., Kraft R.O. et al.
Hemodynamic mechanism for pulse changes seen in occlusive vascular disease.
Surgery 1965; 57: 163.

15. Lewis J.D., Papathanaiou C., Yao S.T., Eastcott H.H.G.
Simultaneous flow and pressure measurements in intermittent claudication.
Br. J. Surg. 1972; 59: 418.

16. Mahler F., Bruner H.H., Fronek A., Bollinger A.
Der Knöchelarteriendruck während reaktiver Hyperämie bei Gefässgesunden und Patienten mit arteriellen Verschlusskrankheit.
Schweiz. Med. Wschr. 1975; 105: 1786.

17. Myhre H.O.
Reactive hyperemia of the human lower limb.
VASA 1975; 4: 227.

18. Storen G.
Calf volume changes during postischemic hyperemia in normal and arteriosclerotic legs.
Scand. J. Clin. Invest. 1967; 20: 147.

19. Strandness D.E., Bell J.W.
An evaluation of the hemodynamic response of the claudication extremity to exercise.
Surg. Gynecol. Obstet 1964; 119: 1237.

20. Strandness Jr. D.E., Sumner D.S.
Non-invasive methods of studying peripheral arterial function.
J. Surg. Res. 1972; 12: 419.

21. Thulesius O.
Simultane Dopplersonographie von Arm-und Beingefässen bei arteriellen Okklusionen.
In: Kriesmann A., Bollinger A. (Hrsg.): Ultraschal-Doppler Diagnostik in der Angiologie. Thieme, Stuttgart 1979.

22. Vandewater J.M., Indech C.D.V., Indech R.B., Randall H.T.
Hyperemic response for accurate diagnosis of arterial insufficiency.
Arch. Surg. 1980; 115: 851.

23. Yao S.T., Hobbs J.T., Irvine W.T.
Ankle systolic pressure measurements in arterial disease affecting the lower extremities.
Brit. J. Surg. 1969; 56: 676.

CHAPTER VII

INDICATIONS FOR FUNCTIONAL EXAMINATION IN PATIENTS WITH PERIPHERAL ARTERIOPATHY.

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VII.1 Introduction

The determination of the blood-pressure at the ankle after exercise or after ischemia has become common practice in vascular surgery, because many authors (1-9) believe that such functional examination provides data that may be of immediate importance for both the diagnosis and the clinical decision making in patients with peripheral atherosclerosis.
Prompted in part by the fact that other authors (10) have recently challenged this view, we have evaluated the data obtained by the reactive hyperemia test in our personal material.
The first question was whether these data supply more information than mere determination of the ankle systolic blood-pressure at rest.
The second question was whether the reactive hyperemia test might provide supplementary or alternative information compared with the results of arteriographic examination, especially in regard to localization of the hemodynamically most important lesions.

Patients and methods

Reactive hyperemia test (RHT)

This test was carried out by the standard technique, using the Doppler equipment, during reactive hyperemia following 4 minutes of total ischemia of the extremity (11). The parameters used were the index at rest (systolic ankle/arm blood-pressure index at rest), the 15-second index (ankle/arm index 15 seconds after cessation of ischemia) and the index gradient (the difference between the index at rest and the 15-second index).

Patients

The investigation comprised two separate studies. In study A, the value of the results of the RHT in determining the severity of the lesions was assessed.
In study B, these results were compared with the angiographic findings.

Study A

In this study, the RHT data were collated for comparison in 4 sub-groups, viz.: group A-I consisting of patients without symptoms or with atypical symptoms (69 extremities), group A-II with typical intermittent claudication and a walking distance of more than 100 meters (119 extremities), group A-III consisting of patients with severe intermittent claudication and a walking distance of less than 100 meters (37 extremities) and group A-IV consisting of patients with rest pain or gangrene (23 extremities).

Study B

The patients in this study were subjected not only to RHT but also to arteriographic examination. On the basis of the arteriogram, the patients were divided into three sub-groups, in each of which the findings were related to the respective RHT data: Group B-I with lesions confined to the aorto-iliac tract (28 extremities), group B-II with lesions limited to the femoro-popliteal tract (49 extremities) and group B-III consisting of patients with lesions in both the aorto-iliac and the femoro-popliteal tracts (35 extremities).

Statistical analysis

The difference in findings between the two groups were analysed by means of the test of Kruskal and Wallis, significance $p < 0.1$.

Results

Study A (Fig. I) The mean index at rest in group A-I was 112.1 $\pm$ 11.6%; that in group A-II, 72.0 $\pm$ 13.9%; that in group A-III, 53.9 $\pm$ 11.8%; and that in group A-IV, 50.4 $\pm$ 16.1%. It was found that all groups differed significantly from each other on the basis of the index at rest ($p < 0.0005$), except as between group A-III and group A-IV.

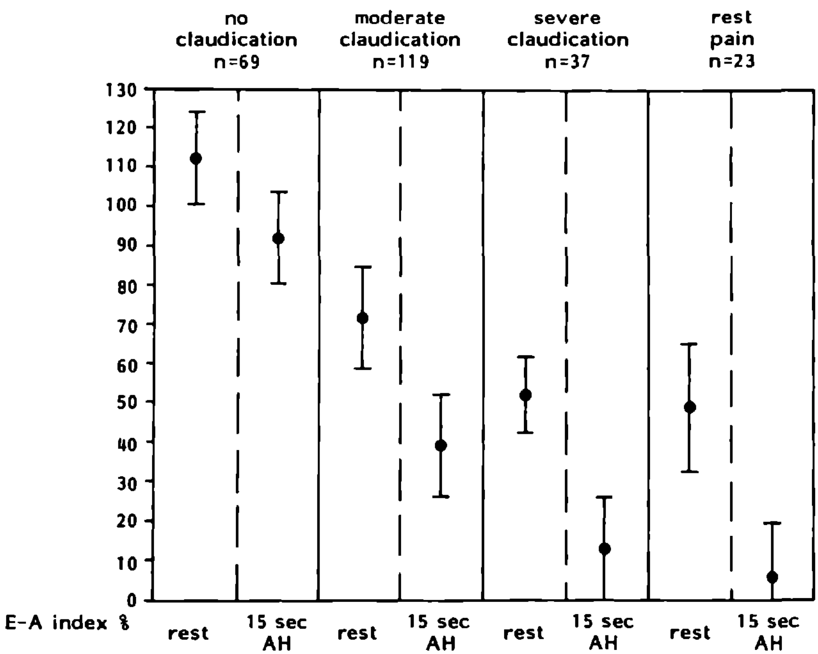

Figure I: The mean and standard deviations of the systolic ankle-arm blood pressure index (EA-Index) at rest and after 15 seconds reactive hyperemia (RH) in 4 groups of clinically divided patients.

The values found for the 15-second index amounted to 92.7 $\pm$ 16.3%, 39.4 $\pm$ 15.2%, 14.1 $\pm$ 14.5% and 7.9 $\pm$ 11.7% respectively in these groups.
On the basis of the 15-second index, also, all groups differed significantly from each other, except again as between group A-III and group A-IV.
The index gradient in group A-I was 19.4 $\pm$ 14.2%, in group A-II 32.6 $\pm$ 11.4%, in group A-III 39.8 $\pm$ 13.3% and in group A-IV 42.5 $\pm$ 19.4%. There were significant differences between the values found for groups A-I and A-II, A-I and A-III and A-II and A-III. There were no significant differences between groups A-II and A-IV and groups A-III and A-IV.

Study B (see Fig. II) The mean index at rest in group B-I amounted to 69.3 $\pm$ 18.2%, in group B-II to 63.8 $\pm$ 14.6% and in group B-III to 56.5 $\pm$ 16.1%.

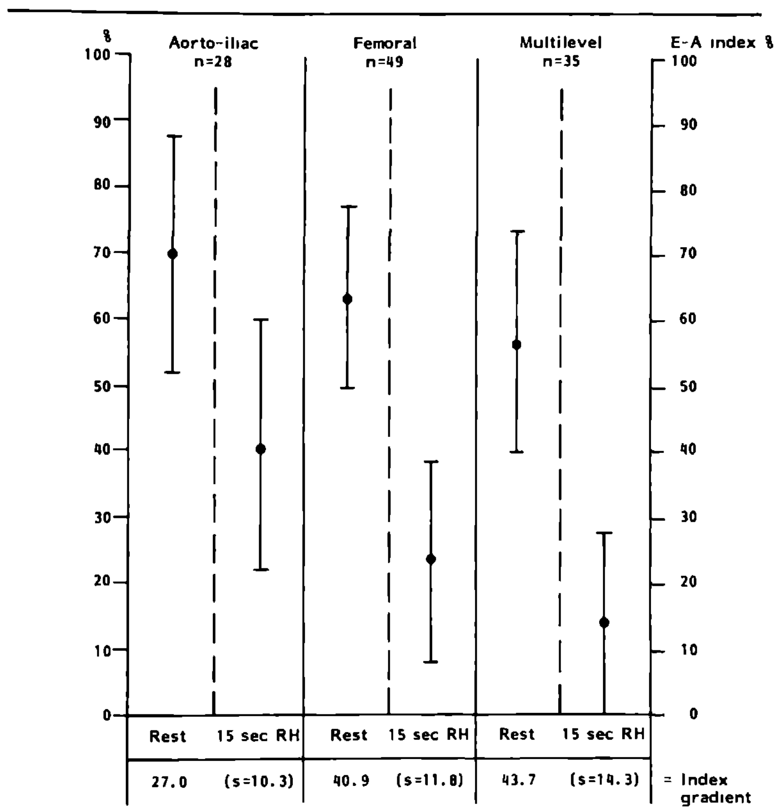

Figure II: The mean and standard deviations (s) of the systolic ankle-arm bloodpressure index at rest, after 15 seconds reactive hyperemia (RH) and of the index gradient in 3 groups of patients divided according to the angiogram.

These three groups just attain significant difference at the $p < 0.1$ level. The mean 15-second index in group B-I was 42.4 ± 18.4%, in groups B-II 22.9 ± 14.2% and in group B-III 13.1 ± 14.1%.
The differences between the three groups were highly significant at the $p < 0.01$ level.
The mean index gradient in group B-I was 27.0 ± 10.3%, in group B-II 40.9 ± 11.8% and in group B-III 43.7 ± 14.3%. The difference between group B-I on the one hand and groups B-II and B-III on the other was also highly significant statistically ($p < 0.0005$).
Groups B-II and B-III were not significantly different.

Discussion

In the treatment of patients with peripheral atherosclerosis, it is of prime importance to be certain that the symptoms are actually due to an arterial lesion.
Second, we attempt to evaluate the severity of the arterial insufficiency as this may determine the need for arterial reconstruction, and in the third place, both for prognosis and the choice of optimal management, it is important to know where the hemodynamically most important lesions are situated. Below, we discuss whether functional examination contributes answers to these questions adequate enough to justify its routine use.

Functional examination may roughly be divided into two groups.
In one, the patient performs some type of exercise and the effect on the blood-pressure at the ankle or on the flow rate is recorded.
The treadmill test is generally used for this purpose (4.7.12-17).
Other less frequently used methods are bicycle ergometry, pedal ergometry, tiptoe exercises and step-ups. In the second group, the reaction of the ankle pressure or of the flow rate to a period of ischemia of the extremity is measured, the so-called reactive hyperemia test (18-24).
The alleged advantage of the treadmill test is that the walking distance can be determined objectively, but the reproducibility of this parameter is poor (14.21.25.26). The advantages of the RHT are that it is better reproducible and provides a standardized degree of stress (11).

Presence or absence of arterial insufficiency

It is clear from numerous investigations that with the aid of the systolic ankle pressure measured at rest (ankle/arm index, ankle/arm blood-pressure gradient), it is possible virtually without exception to distinguish symptoms due to arterial insufficiency from those of a different origin (5, 7.12.15.20.27-38).
In this connection it should be noted that factors such as severe diabetes mellitus, sclerosis of the tunica media and ankle edema, by reducing the compressibility of the arteries, may falsify the measurement of ankle pressure and give values that are too high (38.39). It is only in exceptional cases that an ankle pressure which is normal at rest shows a pathologic fall after exercise or during

reactive hyperemia, and it is only in these odd cases that the functional tests provide supplementary information (5).
In all other cases, measurement of the ankle pressure at rest satisfies the question whether or not arterial insufficiency is involved.
In our study, the results of the RHT did not supply additional information in this respect (Fig. I).

The severity of the arterial insufficiency

In patients with the most severe type of arterial insufficiency, in which the vitality of the extremity is endangered (Fontaine degrees III and IV), there are rarely grounds for extensive further examination. Angiographic examination and, if possible, vascular reconstruction are then indicated.
Nevertheless, examination at rest in itself allows a distinction between the endangered group and patients with only intermittent claudication (15.40-43) and, as our experience with the RHT shows, functional examination provides no additional information. Accordingly, the examination may be omitted in these patients.

In the group of patients with intermittent claudication (Fontaine degree II) on the other hand, it is useful to determine the degree of arterial insufficiency and particularly to record it objectively. This applies to the planning of surgery and to the follow-up of patients, whether operated or not, to assess the degree of progression of the primary disease.
Unfortunately, here too functional examination does not offer distinct advantages over measurement of the ankle pressure at rest as the sole assessment.
As the results of the RHT show (Fig. I), neither the 15-second index nor the index gradient have more discriminative value than the index at rest, which is far easier to determine.
If the treadmill test is used as the functional examination, the walking distance of the patient can be determined more objectively. This parameter is therefore sometimes used to help define the need for surgical intervention (43). We take serious objection to this practice because the reproducibility of the walking distance so determined proves to be poor (14, 21, 25, 26), i.e., it is not a truly objective parameter.
In general, therefore, we may conclude that, in assessing the severity of the vascular insufficiency the routine use of functional examinations such as the treadmill test or the reactive hyperemia test is not indicated.

Localization of hemodynamically important lesions

Several investigators have attempted to localize the hemodynamically most important lesions by means of functional examination. In practice, this amounts to distinguishing between lesions in the aorto-iliac tract and lesions in the femoro-popliteal tract, or identifying a combination of both.

Solitary lesions in the arteries of the crural vessels rarely affect the ankle pressure (28.40) and surgical treatment is rarely necessary in these cases.
Numerous investigators have demonstrated that it is quite possible on the basis of the ankle/arm index at rest to distinguish between occlusions or severe stenoses at one level and those at several levels (8.28.29.44).
On the other hand, it has been found that the ankle pressure at rest does not permit sufficient distinction between patients with lesions mainly or entirely in the aorto-iliac tract and patients whose principle lesions are in the femoro-popliteal tract (12.30.38.45.46).
Although in our study the discrimination between these two groups on the basis of the ankle/arm index at rest was just significant, the 15-second index and the index gradient permitted far better discrimination in this respect. These findings accord with the results obtained by Myhre (20) and Vandewater, et al (47), although the latter authors observed the most important decrease of pressure in the iliac and not in the femoral group as Myhre and we ourselves did. All these authors employed the RHT, although with slightly different techniques.
The results of the investigators who have used other functional tests to locate the chief lesions are not consistent either. Some found the main fall of ankle pressure after exercise in patients with aorto-iliac lesions (8.12.15.48), while others noted no difference or even an opposite finding (20.38). All investigators agree on one point: that, irrespective of the nature and performance of the functional examination carried out, the fall of blood-pressure after exercise or during reactive hyperemia was most pronounced in patients with multilevel lesions.
Although in our study the RHT findings for the group as a whole made it possible to distinguish between aorto-iliac and femoro-popliteal lesions, this finding should be interpreted with caution.
Although the differences between the groups were statistically significant, there was considerable overlap of the values found in the different groups - a finding noted by others (38) - and this may seriously impair their clinical applicability in the evaluation of the individual patient. Further, comparisons with data obtained by angiography have pronounced shortcomings (49.50).

To recapitulate, we believe that in the diagnosis and treatment of patients with symptoms or signs of peripheral arteriopathy, determination of the ankle/arm index at rest, combined with specific history-taking and adequate physical examination, will generally suffice.
Routine supplementary examinations such as the treadmill test or the reactive hyperemia test are unnecessary and stressful for the patients and the examiner, as well as expensive. (10)
Although, to some extent, the reactive hyperemia test may help to localize the hemodynamically most important lesions, this finding is of only limited value in the treatment of the individual patient.
To what extent intra-arterial measurements of the pressure in the femoral artery have more to offer is a question we are currently investigating.

VII.2 ADDENDUM

VII.2.1 Introduction

In chapters VI and VII the correlations are discussed between the ankle-arm blood pressure indices at rest and during PIRH, with the extent of arterial obstructive disease and the localization of hemodynamically significant lesions.
Earlier it was concluded that the most reproducible and valuable parameter of the PIRH test is the point of maximal response of the blood flow or blood pressure, depending on which is measured.
From chapter VI it is concluded that this point of maximal blood pressure response during PIRH had the best correlation with the point of maximal blood pressure response during PERH.
Therefore, this point of maximal response (15 second index) was taken as the most important PIRH parameter in the correlation studies described in chapters VI and VII.
Some authors (for example: Fronek et al, ref. 95, chapter IV) state that the return time of the blood pressure curve to the resting value is of clinical significance.
In a later phase, the return times as calculated from the patients PIRH curves, were correlated with the extent and localization of arterial obstructive disease.
The results of this correlation are discussed below.

VII.2.2 The correlation between the return time and the extent of arterial obstructive disease

Group A1, consisting of 77 extremities with no intermittent claudication, showed an average return time of 50.6 seconds.
Group A2, consisting of 120 extremities with moderate intermittent claudication, showed an average return time of 82.2 seconds.
Group A3, 37 extremities with serious intermittent claudication, had an average return time of 93.6 seconds.
Group A4, 24 extremities with tissue loss or pain at rest had an average return time of 105 seconds.
According to the statistical test of Kruskal and Wallis, all groups differed significantly from each other, with the exception of groups A3 and A4.
In other words, based on the return times, group A1, group A2 and the combination of groups A3 and A4 can be distinquished as separate groups.

VII.2.3 The correlation between the return time and the localization of arterial obstructive disease

Group B1, 36 extremities with only aorto-iliac disease, showed an average return time of 82.5 seconds.
Group B2, 56 extremities with only femoro-popliteal disease, had an average return time of 84.3 seconds.
Group B3, 34 extremities with multiple level disease, showed an average return time of 93.9 seconds.

Based on the return times, no significant difference could be found between the three groups.

VII.2.4 Conclusion

With regard to the clinical classification, it is concluded, that the return time does not provide more information than the other PIRH parameters.
With regard to angiographical classification, the return time does not provide any information.
This justifies using only the minimal blood pressure index during PIRH, for the correlation studies, as was done in our study.
It appears that the return time in a PERH test is also of little or no clinical value (10).

VII.3 Conclusion of chapters V, VI and VII and introduction to chapters VIII and IX.

Based on the findings described in chapters VI and VII, it can be concluded that performing blood pressure measurements at the ankle routinely during PIRH, is unnecessary in patients presenting with symptoms suggestive of arterial insufficiency.
The degree of arterial obstructive disease can be determined adequately by measurement of the ankle blood pressure at rest.
The localization of hemodynamically significant lesions in the arterial tree of the leg must be assessed by other tests.
The first experiences with such a test; the FAP test (direct femoral artery pressure measurements at rest and during PIRH) are described in chapter VIII.
Chapter IX contains the results of a prospective study, using the FAP test in the assessment of the aorto-iliac segment in patients with multiple level, arterial obstructive disease.
The FAP test was chosen following a literature review of all the diagnostic tests available which were described in chapter III.

1. Mackereth M., Lennihan R.
Ultrasound as an aid in the diagnosis and management of intermittent claudication.
Angiology, 1970; 21: 704-713.

2. Thulesius O., Gjöres J.E.
Use of the Doppler shift detection for determining peripheral arterial blood pressure.
Angiology, 1971; 22: 595-603.

3. Strandness D.E., Sumner D.S.
Non-invasive methods of studying peripheral arterial function.
J. Surg. Res. 1972; 12: 419.

4. Lewis J.D., Papathanaiou C., Yao S.T., Eastcott H.M.G.
Simultaneous flow and pressure measurements in intermittent claudication.
Br. J. Surg., 1972; 59: 418.

5. Carter S.A.
Response of ankle systolic pressure to leg exercise in mild or questionable arterial disease.
N. Engl. J. Med., 1972; 287: 578.

6. Yao S.T.
New techniques in objective arterial evaluation.
Arch Surg., 1973; 166: 600.

7. Bollinger A.
Laufbandergometrie und Muskelfunction bei claudicatio intermittens.
Schweiz Med. Wochenstr., 1973; 103: 636.

8. Chamberlain J., Houstey E., MacPherson A.I.S.
The relationship between ultrasound assessment and angiography in occlusive arterial disease of the lower limb.
Br. J. Surg., 1975; 62: 64-67.

9. Fronek A., Coel M., Bernstein E.F.
The importance of combined multi-segmental pressure and Doppler flow velocity studies in the diagnosis of peripheral arterial occlusive disease.
Surgery, 1978; 84: 840-847.

10. Ouriel U., McDonnel A.E., Metz C.E., Zarius C.U.
A critical evaluation of stress testing in the diagnosis of peripheral vascular disease.
Surgery, 1982; 91: 686-693.

11. Verhagen P.F., van Vroonhoven Th.J.M.V.
Ankle pressure changes during reactive hyperemia in peripheral arterial disease.
VASA, 1983; 12: 29-34.

12. Strandness D.E., Bell J.W.
An evaluation of the hemodynamic response of the claudicating extremity to exercise.
Surg. Gynecol. Obstet., 1964; 119: 1237-1242.

13. Larsen O.A., Lassen N.A.
Effect of daily muscular exercise in patients with intermittent claudication.
Lancet II, 1966; 1093.

14. Siggaard-Andersen J., Petersen F.B.
Intermittent claudication. A comparison between subjective and measured claudication walking distance.
Angiology, 1968; 19: 426.

15. Yao S.T.
Hemodynamic studies in peripheral arterial disease.
Br. J. Surg. 1970; 57: 761.

16. Tønnesen N.H.
Late results of the arterial reconstruction evaluated by exercise blood flow measurement.
Scand. J. Clin. Lab. Invest., 1972; 29: 163.

17. Lennihan R., Mackereth M.A.
Ankle blood pressures as a practical aid in vascular practice.
Angiology, 1975; 26: 211.

18. Hillestad L.K.
The peripheral blood flow in intermittent claudication.
V Plethysmographic studies. The significance of the calf blood flow at rest and in response to timed arrest of circulation.
Acta Med. Scand., 1963; 174: 23.

19. Ehringer H.
Die reaktive Hyperämie nach arterieller Sperre.
In: Messmethoden bei arterieller Durchblutungsstörungen.
(Eds Bollinger A., Brunner V.) Huber, Bern, 1971; p 20-33.

20. Myhre H.O.
Reactive hyperemia of the human lower limb. Measurement of postischaemic blood flow velocity in controls and in patients with lower limb atherosclerosis.
VASA, 1975; 4: 145-149.

21. Baker J.P.
Poststress Doppler ankle pressures. A comparison of treadmill exercise with two other methods or induced hyperemia.
Arch. Surg., 1978; 113: 1171-1173.

22. Hummel B.W., Hummel B.A., Mowbry A., Maixner W., Barnes R.W.
Reactive hyperemia vs treadmill exercise testing in arterial disease.

Arch. Surg., 1978; 113: 95-98.

23. Verhagen P.F., van Vroonhoven Th.J.M.V.
De reactieve hyperemieproef; eenvoudig uitvoerbare methode om de perifere arteriële bloedstroom onder belasting te onderzoeken.
Ned. T. Geneesk., 1981; 125: 466-469.

24. Keagy B.A., Pharr W.F., Thomas D., Bowes D.E.
Comparison of reactive hyperemia and treadmill tests in the evaluation of peripheral vascular disease.
Am. J. Surg., 1981; 142: 158-161.

25. Hillestad L.K.
The peripheral blood flow in intermittent claudication IV. The significance of the claudication distance.
Acta Med. Scand., 1963; 173: 467.

26. Clyne C.A.C., Tripolitis A., Jamieson J.W. et al.
The reproducibility of the treadmill walking test for claudication.
Surg. Gynaecol. Obstet., 1979; 149: 727-728.

27. Winsor T.
Influence of arterial disease on the systolic blood pressure gradients of the extremity.
Am. J. Med. Sci., 1950; 220: 117.

28. Carter S.A.
Indirect systolic pressures and pulsewaves in arterial occlusive disease of the lower extremities.
Circulation, 1968; 37: 624.

29. Carter S.A.
Clinical measurement of systolic pressures in 12 limbs with arterial occlusive disease.
JAMA, 1969; 207: 1869.

30. Sumner D.S., Strandness D.E.
The relationship between calf blood flow and ankle blood pressure in patients with intermittent claudication.
Surgery, 1969; 65: 763.

31. Yao S.T., Hobbs J.T., Irvine W.T.
Ankle systolic pressure measurements in arterial disease affecting the lower extremities.
Br. J. Surg., 1969; 56: 676.

32. Bollinger A., Mahler F., Zehender O.
Kombinierte Druck- und Durchflussmessungen in der Beurteilung arterieller Durchblutungsstörungen.
Dtch. Med. Wochenschr., 1970; 95: 1039.

33. Yao S.T., Needham T.H., Gourmoos C., Irvine W.T.

A comparative study of strain-gauge plethysmography and Doppler ultrasound in the assessment of occlusive arterial disease of the lower extremities.
Surgery, 1972; 71: 4.

34. Bienmuller H.
Frühdiagnostik obliterierender Gefässerkrankungen der unteren Gliedmassen.
Med. Klin., 1975; 20:, 1139-1147.

35. Mahler F., Brunner H.H., Fronek A., Bollinger A.
Der Knochelarteriendruck während reaktiven Hyperämie Gefässgesunden und Patienten mit arterieller Verschlusskrankheit.
Schweiz. Med. Wochenschr., 1975; 105: 1786-1788.

36. Barras J.P., Bollinger r., Buholzer F., Gruntzig A., Butti P.
Direkte poststenotische Blutdruckmessung in den Knöchelarterien.
VASA, 1976; 5: 208.

37. Schoop W.
Die Ultraschall-Doppler Methode in der Diagnostik der arteriellen und venösen Störungen in den Extremitäten.
Internist, 1976; 17: 580.

38. Kriesman A., Neiss A., Reipert C., Rädler M., Rupp N.
Parameter-analyse bei Ultraschall-Doppler Druckmessung vor und nach Ischämieprovokation.
In: Ultraschall-Doppler Diagnostik in der Angiologie. 1979.
Eds. Kriesman, A. und Bollinger A. Thieme Verlag. Stuttgart.

39. Bernstein E.F., Fronek A.
Current status of non-invasive tests in the diagnosis of peripheral arterial disease.
Surgical Clinics of North America, 1982; 62: 473.

40. Strandness D.E.
Abnormal exercise responses after successful reconstructive arterial surgery.
Surgery, 1966; 59: 325.

41. Thulesius O.
Beurteilung des Schweresgrades arterieller Durchblutungs-störungen mit dem Doppler Ultraschall-Gerät.Brunner V., Huber, Bern, 1971; 44-47.

42. Lennihan R., Mackereth M.A.
Ankle pressures in arterial occlusive disease involving the legs.
Surgical Clinics of North-America, 1973; 53: 657.

43. Raines J.K., Darling R.C., Buth J., Brewster D.C., Austen W.G.
Vascular laboratory criteria for the management of peripheral vascular disease of the lower extremities.

Surgery, 1976; 79: 21.

44. Ludbrook J.
Collateral artery resistance in human lower limb.
J. Surg. Res., 1966; 6: 423.

45. Fronek A., Johansen K.H., Dilley R.B., Bernstein E.F.
Non-invasive physiologic tests in the diagnosis and characterization of peripheral arterial occlusive disease.
Am. J. Surg., 1973; 126: 205.

46. Quin R.O., Evans D.H., Fyfe T., Bell P.R.F.
Evaluation of indirect blood pressure measurement as a method of assessment of peripheral vascular disease.
J. Cardiovasc. Surg., 1977; 18: 109.

47. Vandewater J.M., Indech C.D.V., Indech R., Randall H.
Hyperemic response for accurate diagnosis of arterial insufficiency.
Arch. Surg., 1980; 115: 851.

48. Buth J.
Doppler bloeddrukmeting aan de enkel bij perifeer arterieel vaatlijden: een nieuwe aanwinst in de vaatchirurgie.
Ned. T. Geneesk., 1975; 119: 388.

49. Moore W.S., Hall A.D.
Unrecognized aorto-iliac stenosis, a physiologic approach to the diagnosis.
Arch. Surg., 1971; 103: 633-638.

50. Brener B.J., Raines J.K., Darling R.C., Austen W.G.
Measurement of systolic femoral arterial pressure during reactive hyperemia, an estimate of aorto-iliac disease.
Circulation, 1974; Vol 49/50, Suppl. II: 259-267.

CHAPTER VIII

DIRECT FEMORAL ARTERY PRESSURE MEASUREMENTS AT REST AND DURING REACTIVE HYPEREMIA IN THE EVALUATION OF THE AORTO-ILIAC SEGMENT.

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VIII.1 Introduction

The assessment of the aorto-iliac segment in patients with, what angiographically seems to be multilevel arterial occlusive disease, remains a difficult problem for the vascular surgeon.
The results in patients in whom only an inflow procedure is performed are frequently disappointing, no improvement being reported in up 35% of cases (1-11).
A simple reliable method for measuring the hemodynamic importance of aorto-iliac lesions would therefore be of great help to select the correct procedure.
It has been suggested (12.13) that direct femoral artery pressure (FAP) measurements can help to distinguish between important and non-important occlusive lesions seen on a angiogram.
From an extensive survey of the literature (12-29), however, it became soon apparent that no uniform FAP criteria for clinical success existed. The aim of this study was therefore to find FAP criteria which would be clinically useful.

Patients and methods

Femoral artery pressure measurements

Under local anesthesia the common femoral artery was cannulated with a 40 - 1.1 mm needle and the radial or brachial artery was cannulated by a viggo needle (1.2 mm - 45 mm).
Both needles were connected to lockable extension tubes (length 100 cm, diameter 1 - 2 mm), and these tubes were connected to Statham disposable diaphragm domes with autoflush.
Both systolic pressures were recorded simultaneously using a Siemens Sirecust recorder and a hard copy was made of the pressure readings.
After measurements were made at rest, a tourniquet was placed around the thigh and total arterial occlusion was achieved for 4 minutes.
During the reactive hyperemia (PIRH) following release of the arterial circulation again systolic pressures were recorded simultaneously.
The Groin-Arm Index (GA Index) at rest and after 15 seconds (GA Index 15) were determined. The 15-second point was chosen, because then usually the lowest systolic blood pressure was recorded.
The Index Gradient (IG) was defined as the difference between the GA Index at rest and the GA Index after 15 seconds RH.
Two groups of patients were studied.

Group A

(38 extremities) consisted of patients in whom either a proximal or a distal arterial reconstruction was performed for angiographically multilevel atherosclerotic disease, based on history, physical examination, Doppler derived ankle pressures and arteriography.
The results of the femoral artery pressure measurements did not, however, contribute to the decision whether a proximal or a distal reconstruction was to be performed.
Patients were evaluated again at 6 months after the operation and the results of the direct femoral artery measurements were correlated with the follow-up data.

Group B

Represented 54 extremities from patients with either multilevel or only aorto-iliac atherosclerotic disease.
In this group the GA Index after 60 seconds reactive hyperemia (GA Index 60) and the GA Index during arterial occlusion (GA Index Occ) were determined additional to the GA Index 15, the GA Index at rest and the index-gradient.
The results of single plane angiography were correlated with the data from femoral artery pressure measurements.
A subdivision in the group of patients was made between minimal to moderate aorto-iliac disease (stenosis < 70% on the angiogram) and radiologically significant aorto-iliac disease (stenosis > 70% or total occlusion).

Results

There were no complications secondary to a FAP study with PIRH. During the following operation we did not see hematomas that made dissection more troublesome, all patients considered the 4 minutes tourniquet occlusion bearable.

Group A

A1 Extremities with a GA Index at rest < 70% (n=3)
The three extremities in this group underwent a proximal reconstruction. All three showed improvement both subjectively and objectively.

A2 Extremities with a GA Index at rest between 70% and 90% (n=13)
Five of these extremities had an IG which was $\geq$ 20%.
Four of these five extremities underwent a proximal reconstruction of which three improved.
The fifth extremity improved after a femoro-popliteal bypass.
Eight extremities had an IG < 20%, five of these eight underwent a proximal reconstruction of which only one improved. The other three underwent a distal reconstruction and all three showed improvement.

A3 Extremities with a GA Index at rest > 90% (n=22)
In five extremities an IG $\geq$ 20% was found. In three a proximal reconstruction was performed with an improvement in one, and in two a distal reconstruction was done which both gave a good result.
The other seventeen extremities in this group had an IG < 20%.
In seven a proximal reconstruction was performed and none of these seven improved.
In ten a distal reconstruction was done, eight improved, two did not, due to early graft thrombosis. These two were both femoro-crural bypasses.

Group B

The results of the correlation between angiography and direct femoral artery pressure measurements are summarized in Table I.
In 13 extremities radiologically significant disease was found.
The aorto-iliac lesions of 41 extremities were thought to be minimal.
The mean GA Index at rest was 81% in the significant group, and 99% in the minimal group.
After 15 seconds of reactive hyperemia these mean values were 60% and 80% respectively, while after 60 seconds of reactive hyperemia the mean GA Index was 76% in the radiologically significant and 93% in the radiologically minimal group.
The mean IG was 21% in the significant versus 11% in the minimal group.
In the significant group 31% had an IG $\geq$ 20%. In the minimal group this percentage was 9%.

this percentage was 9%.
Finally the mean GA Index Occ in the significant and minimal group was 84% and 102% respectively.
Although the differences for the mean values between the two groups are quite considerable, the overlap as shown by the upper and lower limits is too great to permit useful statistical evaluation.

TABLE 1.—*Mean values and upper and lower limits of parameters from direct femoral artery pressure measurements at rest and during reactive hyperemia in 54 extremities, divided in a group with minimal aorto-iliac and a group with significant aorto-iliac disease.*

	Significant (n=13)		Minimal (n=41)	
	Mean	Upper and lower limit	Mean	Upper and lower limit
GA Index at rest	81%	104-52%	99%	198-34%
GA Index^{15}	60%	86-39%	88%	175-37%
GA Index^{60}	76%	96-54%	93%	182-32%
GA Index^{Occ}	84%	105-60%	102%	198-30%
Index Gradient	21%	32-13%	11%	38- 0%

GA Index=Groin-Arm index=systolic femoral-brachial pressure Index, at rest, after 15 and 60 seconds reactive hyperemia and during tourniquet occlusion.

Index Gradient–Difference between GA Index at rest and GA Index^{15}.

Discussion

So-called multilevel atherosclerotic disease is said to be present in the majority of patients coming to surgery (29).
This -'being multilevel'- is in most cases a suspicion based on angiography. It is therefore in the majority of patients necessary to get extra information about the hemodynamic importance of inflow disease.
A wide variety of non-invasive tests have been proposed to assess the hemodynamic severity of occlusive disease at different levels and thereby to aid in prediction of outcome in patients with multilevel disease (12). However many authors (12.29) believe FAP studies are, although invasive, superior in predictive value.
In reviewing the rather extensive literature (12-29) there appears to be no uniformity of criteria.
Certain vascular laboratories have changed their criteria in the course of time (13.26).
The explanation for the absence of uniform criteria is probably the fact that different gold standards to compare the methods with were used and that an often used gold standard -namely angiography- has a substantial intrinsic unreliability (30).
Since relieving or at least decreasing the complaints of the patients is our main goal we have to find our FAP criteria in the correlation with clinical data and not with angiographical data.
By doing so Flanigan et al (12) using receiver operator characteristic analysis found a very accurate FAP criterion for clinical success.
This criterion they called %ΔF.B.I., meaning, the percentage decrease of the femoro-brachial index during maximal vasodilatation after intra-arterial papaverine injection.
All extremities with a %ΔF.B.I. of $\geq$ 0.15 improved following a proximal reconstruction and no extremities with a %ΔF.B.I. < 0.15 improved following a proximal reconstruction.
Our results, now to be discussed, are in many ways quite similar to the results of Flanigan et al (12).

Single plane aorto-iliac angiography proved to be 80% sensitive, 50% specific and 58% accurate in relation to predicting post-operative hemodynamic improvement. The positive predictive value was 36% and the negative predictive value 87%.
The group extremities with a GA Index at rest > 70% (group A2 and A3) consisted of 19 proximal reconstructions.
The overall clinical failure rate of those 19 reconstructions was a disappointing 73%.
In the group with an IG $\geq$ 20%, four out of seven extremities improved after a proximal reconstruction.
Three extremities showed no improvement, however two out of these three had a GA Index at rest > 90%.
So in the group with a GA Index at rest between 70% and 90% the clinical success rate was 75%, when the IG was $\geq$ 20%.

When we consider the results of the study in group B, we must conclude that, although the mean values of the used parameters differ in the

minimal and significant group, the overlap is considerable. However we can make some interesting observations from these data. When the IG was < 20%, 92% showed no improvement after a proximal reconstruction and patients who benefitted from a proximal reconstruction had an IG $\geq$ 20% in 80%.
So we can presume that patients with significant aorto-iliac disease are to be found in the group with an IG $\geq$ 20%.
In our study, however only 31% of the aorto-iliac segments considered to be significantly diseased, had an IG $\geq$ 20%. In 69% therefore the aorto-iliac segment was considered to be significantly diseased, while according to the FAP studies there was only minimal to moderate disease. It appears that it is uncommon for an observer of an angiogram to under-estimate the disease, because in the minimal diseased group we found 91% to have an IG < 20%. So in only 9% the disease on the angiogram was under-estimated.

Conclusions

The conclusions from our study can be summarized as follows.

First of all, the observer of an aorto-iliac angiogram is inclined to overestimate the hemodynamic importance of atherosclerotic occlusive disease. This could lead to diagnosing multilevel disease too often and performing too many proximal reconstructions.
The question even rises whether the statement, mentioned above (29), that multilevel occlusive disease is present in the majority of patients coming to surgery is, hemodynamically spoken, actually correct.
Secondly, we agree with other authors (12-29), that FAP studies are an accurate way to assess the hemodynamic importance of aorto-iliac disease.
In the third place, we believe that when the GA Index at rest is < 70%, no additional PIRH test is necessary and one can expect a good clinical result from a proximal reconstruction.
When the GA Index at rest is > 70%, it is advisable to add a PIRH test, as described. When the IG is < 20%, the chance to achieve clinical improvement by performing a proximal reconstruction, is almost nil.
When the IG is > 20% the chance to achieve clinical improvement rises sharply and was overall approximately 60%.
In the subgroup with a GA Index at rest between 70% and 90% this percentage was 75% (3/4).
Last of all, we think these criteria need to be confirmed in a prospective study, and such a study has been started now.

VIII.2. ADDENDUM

Chapter X contains the results of a recalculation of the data described in chapter VIII.
The results are expressed more in terms of accuracy, specificity and sensitivity of the used method, as compared to a goldstandard.
On top of that a receiver-operator characteristic curve analysis of the index gradient has been performed at a later date, the results of that analysis are also described in chapter X.
A receiver operator characteristic curve analysis (ROC analysis) expresses a dynamic relation between specificity and sensitivity (or respectively 100% minus % False + and 100% minus % False -) of a certain test parameter, compared to a specific standard of evaluation (Fig. 1, page 129).
In this study the test parameter was the index gradient (IG). So for a number of values of the test parameter (IG 10%, 15%, 20% and 25%), the specificity and sensitivity in the detection of significant aorto-iliac disease, with the 6 month postoperative result as the goldstandard, were calculated. By means of a ROC analysis the best IG (with the highest specificity and sensitivity) can easily be determined. The ROC analysis confirmed that an IG of 20% has the highest sensitivity and specificity in the detection of significant aorto-iliac disease.

1. Imparato A.M., Sanoudos G., Epstein H.Y., Abrams R.M., Beranbaum E.R.
Results in 96 aorto-iliac reconstructive procedures.
Preoperative angiographic and functional classifications used as prognostic guides.
Surgery 1970, 68, 610-616.

2. Perdue G.D., Long W.D., Smith R.B.
Perspective concerning aorto-femoral arterial reconstruction.
Ann Surg 1971, 173, 940-944.

3. Mozersky D.J., Sumner D.S., Strandness D.E.
Longterm results of reconstructive aorto-iliac surgery.
Am. J. Surg. 1972, 123, 503-509.

4. Edwards W.H., Wright R.S.
A technique for combined aorto-femoral-popliteal arterial reconstruction.
Ann. Surg. 1974, 179, 572-579.

5. Royster R.S., Lynn R., Mulcare R.J.
Combined aorto-iliac and femoro-popliteal occlusive disease.
Surg. Gynecol Obstet 1976, 143, 949-952.

6. Jones A.F., Kempczinski R.F.
Aorto-femoral bypass grafting, a reappraisal.
Arch. Surg. 1981, 116, 301-305.

7. Hill D.A., McGrath M.A., Lord R.S.A., Tracy G.D.
The effect of superficial femoral artery occlusion on the outcome of aorto-femoral bypass for intermittent claudication.
Surgery 1980, 87, 133-136.

8. Sumner D.S., Strandness D.E.
Aorto-iliac reconstruction in patients with combined iliac and superficial femoral arterial occlusion.
Surgery 1978, 84, 348-355.

9. O'Donnell T.F., Lahey S.J., Kelly J.J. et al.
A prospective study of Doppler pressures and segmental plethysmography before and following aorto-femoral bypass.
-Implications for predicting success and for adopting a uniform method of classifying arterial disease-
Surgery 1979, 86, 120-128.

10. Bone G.E., Hayes A.C., Slaymaker E.E., Barnes R.W.
Value of segmental limb blood pressure in predicting results of aorto-femoral bypass.
Am. J. Surg. 1976, 132, 733-738.

11. Garrett W.V., Slaymaker E.E., Heintz S.E., Barnes R.W.
Intra-operative prediction of symptomatic result of aorto-femoral

bypass from changes in ankle pressure index.
Surgery 1977, 82, 504-509.

12. Flanigan D.P., Williams L.R., Schwartz J.A., Schuler J.J., Gray B.
Hemodynamic evaluation of the aorto-iliac system based on pharmacologic vasodilatation.
Surgery 1983, 93, 709-714.

13. Brener B.J., Raines J.K., Darling R.C., Austen W.G.
Measurement of systolic femoral arterial pressure during reactive hyperemia; an estimate of aorto-iliac disease.
Circulation 1974, 49-50 (Suppl II): 259-266.

14. Demorais D., Johnston K.W.
Assessment of aorto-iliac disease by non-invasive quantitative Doppler waveform analysis.
Br. J. Surg. 1981, 68, 789-792.

15. Haimovici H., Escher D.J.
Aorto-iliac stenosis; diagnostic significance of vascular hemodynamics.
Arch. Surg. 1956, 72, 107-117.

16. Weismann R.E., Upson J.F.
Intra-arterial pressure studies in patients with arterial insufficiency of the lower extremities.
Ann. Surg. 1963, 157, 501-506.

17. Wesolowski S.A., Martinez A., Domingo R.T. et al
Indication for aorto-femoral arterial reconstruction.
A study of borderline risk patients.
Surgery 1966, 60, 288-298.

18. Sako Y.
Papaverine test in peripheral arterial disease.
Surgical Forum 1966, 17, 141-143.

19. Moore W.S., Hall A.D.
Unrecognized aorto-iliac stenosis; a physiologic approach to the diagnosis.
Arch. Surg. 1971, 103, 633-638.

20. Lorentsen E., Hoel B.L., Hol R.
Evaluation of the functional importance of atherosclerotic obliterations in the aorto-iliac artery by pressure-flow measurements.
Acta Med. Scand. 1972, 191, 399-403.

21. Quin R.O., Evans D.H., Bell P.R.F.
Hemodynamic assessment of the aorto-iliac segment.
J. Cardiovasc. Surg. 1975, 16, 586-589.

22. Castaneda -Zuniga W., Knight L., Formanek A. et al

Hemodynamic assessment of obstructive aorto-iliac disease.
Am. J. Roentgenol. 1976, 127, 559-561.

23. Bardach G.
Eine neue methode zur direktmessung des Aortofemoralen Druckgradienten im Rahmen der translumbalen Aortographie.
Forschr. Geb. Rontgenstr. nuklearmed. 1978, 128, 317-318.

24. Leveson S.H., Guillou P.J., Terry H.J., Glanville J.N., Kester R.C.
Pulse pressure wave analysis in the diagnosis of aorto-iliac disease.
Ann. Surg. 1978, 187, 161-165.

25. Udoff E.J., Barth K.H., Harrington D.P.
Hemodynamic significance of iliac artery stenosis:
Pressure measurements during angiography.
Diagnostic Radiology 1979, 132, 289-293.

26. Brewster D.C., Waltman A.C., O'Hara P.J., Darling R.C.
Femoral artery pressure measurements during aortography.
Circulation 1979, 60 (Suppl I): 120-124.

27. Evans D.H., Quin R.O., Bell P.R.F.
The significance of blood pressure measurement in patients with peripheral vascular disease.
Br. J. Surg. 1980, 67, 238-241.

28. Flanigan D.P., Gray B., Schuler J.J., Schwartz J.A., Post K.W.
Correlation of Doppler-derived high thigh pressure and intra-arterial pressure in assessment of aorto-iliac occlusive disease.
Br. J. Surg. 1981, 68,423-425.

29. Brewster D.C., Perler B.A., Robison J.G., Darling R.C.
Aorto-femoral graft for multilevel occlusive disease.
Predictors of success and need for distal bypass.
Arch. Surg. 1982, 117, 1593-1600.

30. Bruins-Slot H., Strijbosch L., Greep J.M.
Intra-observer variability in single plane aortography.
Surgery 1981, 90, 497-503.

CHAPTER IX

CRITERIA FROM INTRA-ARTERIAL FEMORAL ARTERY PRESSURE MEASUREMENTS COMBINED WITH REACTIVE HYPEREMIA TO ASSESS THE AORTO-ILIAC SEGMENT; A PROSPECTIVE STUDY.

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Introduction

Direct femoral artery pressure measurements (FAP) combined with intra-arterial papaverine injection (1) or postischemic reactive hyperemia (2.3) (PIRH), to mimic exercise, are attractive ways of assessing the aorto-iliac segment, especially in multilevel disease. Although not completely non-invasive, there is probably no test superior to FAP studies (1.4.5.6).
However, when we review the reports of authors who used FAP studies, there is a lack of uniformity in the criteria used (1.2.3.5.7-19), mainly because the gold standard to compare the method with either differs among the authors or is angiography, a method with considerable intra- and inter-observer variability.
In a previous retrospective study (20), we established criteria for detection of significant stenoses by comparing results of FAP studies (with PIRH) with 6 month postoperative clinical results in patients with angiographically proven multilevel disease.
From the results we concluded that hemodynamically important aorto-iliac disease existed when: The femoro-brachial systolic pressure index at rest (GA Index at rest) is below 70% or when the difference (Index Gradient = IG) between the GA Index at rest and the lowest Index during RH (GA Index 15) is more than 20%.
Aorto-iliac disease was found to be minimal when this IG is less than 20%, provided the GA Index at rest is more than 70%.
The next step was to use these criteria in a prospective way. The results of this study are presented here.

Patients and methods

Femoral artery pressure measurements

Under local anesthesia the common femoral artery was cannulated with a 40-1.1mm needle and the radial or brachial artery was cannulated by a viggo needle (1.2 mm-45 mm).
Both needles were connected to lockable extension tubes (length 100 cm, diameter 1-2 mm), and these tubes were connected to Statham disposable diaphragm domes with autoflush.
Both systolic pressures were recorded simultaneously using a Siemens Sirecust recorder, and a hard copy was made of the pressure readings.
Reactive hyperemia was achieved by a tourniquet placed around the thigh and four-minute total arterial occlusion was caused by inflating the tourniquet.
During reactive hyperemia following deflation of the tourniquet systolic pressures were again recorded simultaneously.

The groin-arm systolic pressure Indices (GA Index) were determined at rest and after fifteen and sixty seconds PIRH (GA Index 15 and GA Index 60 respectively).
The fifteen-seconds point was chosen because the lowest pressure is measured at that time.
The sixty-seconds point was chosen to calculate the Return Time Index (RTI), which was defined as the difference between the GA Index at

rest and the GA Index 60.
The Index Gradient (IG) was defined as the difference between the GA Index at rest and the GA Index 15.

FAP studies were performed on 45 patients. A proximal reconstruction group A and a distal reconstruction group B.
When the GA Index at rest was less than 70% or when the GA Index at rest was more than 70% and the IG was more than 20%, the FAP study was considered to be positive as to presence of significant aorto-iliac disease.
When the GA Index at rest was more than 70% and the IG less than 20% the FAP study was considered to be negative and no significant aorto-iliac disease was assumed to be present.
In three cases the GA Index at rest was more than 90%, in two of these three an additional PIRH test was not performed and the GA Index at rest alone was considered an indication to perform a distal reconstruction (FAP study negative).

Group A

A proximal reconstruction was performed in 27 symptomatic extremities (22 patients).
This included: 16 aorto-femoral- and 4 aorto-iliac reconstructions, 5 intraluminal angioplasties of the iliac segment, one femoro-femoral bypass and one thromboendarterectomy of the common iliac artery. Eight of these proximal reconstructions were performed although the FAP study was negative, because there was associated aneurysmal disease of the aorto-iliac segment.
Angiographically significant multilevel stenoses were thought to be present in 45% of the extremities; the other 55% had multilevel irregularities, the atherosclerotic disease in the aorto-iliac segment being the more severe.

Group B

A distal reconstruction was performed in 23 patients.
All patients had angiographically diseased aorto-iliac segments and occlusions or near occlusions of the superficial femoral artery. All these patients had negative FAP studies.
The 23 distal reconstructions consisted of 21 above- or below knee venous- or P.T.F.E. femoropopliteal bypasses as well as 2 femorocrural bypasses, one combined with a thromboendarterectomy of the anterior tibial artery.

All patients were evaluated 6 months postoperatively.
Categorization of a patient in the improved group required a history of an unlimited or a clearly improved walking distance or absence of pain at rest (subjective improvement).
A postoperative increase in ankle-arm systolic pressure index of at least 10% and healing of ischemic ulcers when they were present preoperatively (objective improvement) was also required.
When a patient showed only objective or subjective improvement, this

was noted as such.

Results

There were no complications of the FAP studies.
The dissection of the groin was not more troublesome after a FAP study, because compression after the procedure prevented hematomas.
The four-minute tourniquet occlusion was well tolerated by all patients.

Group A

In this group 27 extremities underwent a proximal reconstruction. In 19 extremities the FAP study was positive, 18 extremities were improved both subjectively and objectively, and one only subjectively by a proximal reconstruction.
Eight extremities had a negative FAP study.
Five of these eight extremities showed no improvement after a proximal reconstruction.
The other three extremities showed improvement, however one only subjectively and another had a rather high IG of 17%.

Group B

In this group 23 extremities underwent a distal reconstruction.
All this extremities had negative FAP studies. There were no extremities with a positive FAP study that underwent a distal reconstruction.
When the FAP study showed no significant aorto-iliac disease, all femoropopliteal bypasses (n=20) with a good crural run-off gave clinical improvement.
In only one case there was only subjective improvement.
Three distal reconstructions occluded in the immediate postoperative period. Two were femorocrural bypasses for limb salvage, and one had to be combined with a thromboendarterectomy of the anterior tibial artery.
The third was a femoropopliteal bypass. However, there were calcifications at the distal anastomosis site and severely atherosclerotic crural vessels.
These three distal reconstructions occluded in the immediate postoperative period, most likely because of outflow disease and not because of undetected inflow disease.

The results of the calculation of the RTI from the GA Indices 60 in both the proximal and distal group were as follows:
The mean value in the proximal group was 10.7%, with an upper and lower limit of 23% and 1% respectively.
The mean value in the distal group was 2.5% with an upper and lower limit of 8% and 0% respectively.
The scatter around the mean value was too great, to allow useful statistical analysis.

Discussion

Since multilevel disease in many series is said to be the most common pattern of atherosclerotic occlusive disease (21-32), the decision to perform a proximal, distal or combined procedure is a frequent clinical problem.
Previously reported experience has shown that up to 25% of patients with multilevel disease ultimately undergo associated distal reconstructions after a proximal reconstruction (22.25.27.29.31.33-36).
The problem of what to do in multilevel disease cannot be solved by the interpretation of an angiogram, because of the well-known inter- and intra-observer variability in interpretation (37.38.39).
Numerous non-invasive examinations and hemodynamic variables have been recommended to assess the aorto-iliac segment or predict the outcome of proximal reconstruction as well as to predict the need for additional distal reconstruction.
These include: femoral artery Doppler wave form analysis (40.44), Doppler derived thigh blood pressure measurements (33.37.41.44.45), femoral artery pulsatility index (40.42.46), segmental pulse volume recording (48), femoral pressure wave form analysis (16.49), and determination of isotope transit times (50).
All these tests and variables show some correlation with angiography or FAP studies, but no general agreement exists as to their accuracy and usefulness.
Brewster et al (6) did an extensive analysis of 42 variables to predict the outcome of a proximal reconstruction.
The 42 variables were divided into 4 categories:
- 1. History and physical examination.
- 2. Preoperative angiogram (with FAP studies).
- 3. Preoperative non-invasive vascular laboratory data.
- 4. Intraoperative factors.

Only 12 of these 42 variables had some predictive value. The most accurate to assess the aorto-iliac segment appeared to be FAP studies with PIRH (91% positive predictive value).
Among those 12 variables there were only 3 non-invasive vascular laboratory criteria (out of 14 criteria derived from segmental pressure and pulse volume data) that reached a significant predictive value. These 3 variables were Thigh-Brachial Pressure Index (TPI), thigh-ankle pressure index (ΔP) and ,ΔP divided by brachial pressure, a variable called Index Run-off Resistance (IRR).
The TPI is not a very useful criterion, because the width of the cuff and the level at which the cuff is applied all influence the results which are therefore not consistent.
The ΔP and IRR are more useful parameters, however, mainly to assess distal disease.
Flanigan et al (1) using FAP studies with intra-arterial papaverine injection proposed as criterion the %ΔF.B.I. being the maximal percentage drop in femoro-brachial pressure index after papaverine injection.
A cut-off point 0.15 was derived from receiver-operator characteristic analysis.

This %ΔF.B.I. proved to be 95% accurate in assessing the aorto-iliac segment.
Brewster et al (2) using FAP studies with PIRH like we did, used as criterion for significant aorto-iliac disease a drop in FAP of more than 15% during PIRH, or a femoro-brachial FAP gradient at rest of more than 5 mm of mercury. When this criterion was positive, 96% of patients receiving a proximal reconstruction had satisfactory relief of symptoms despite uncorrected distal disease in the majority.
In contrast, 57% of patients undergoing a proximal reconstruction were unrelieved of symptoms when the criterion was negative.
Our data confirm these findings when using as criteria for significant aorto-iliac disease a GA Index at rest less than 70% or, in case the GA Index at rest was more than 70%, an IG of more than 20%. When we assume that the half-year postoperative result of a reconstruction is an indicator of the presence or absence of hemodynamically important aorto-iliac disease, the following conclusions can be drawn.
Aorto-iliac disease was present preoperatively when a proximal reconstruction gives clinical improvement.
Aorto-iliac disease was absent preoperatively when a proximal reconstruction did not give clinical improvement or when a distal reconstruction does give clinical improvement, without occluding in the first half-year postoperatively.
The presence or absence of aorto-iliac disease can then be put against the FAP study data in a binary table.
The used FAP criteria were 76% sensitive, 100% specific and 88% accurate. The positive predictive value is 100% and the negative predictive value 80%.
When we leave out the three distal reconstructions that occluded in the immediate postoperative period, probably because of an obstructed outflow tract, the following values can be calculated : sensitivity 86%, specificity 100%, accuracy 93%, positive predictive value 100% and negative predictive value 89%.

We have to re-emphasize that only half-year postoperative results were considered and no data about long-term patency in the distal group were considered.
From patency studies (51) of distal reconstructions, however, we know that most occlusions occur in the first half-year postoperatively and therefore we believe that half-year postoperative results are an important indication for the long-term patency.
This believe was strengthened by the finding of Brewster et al (2), who performed three distal reconstructions despite a positive FAP study. The three grafts occluded within 14 months and two of these three within 4 months.
Only one occlusion of a femoropopliteal bypass was seen in our material. This occlusion took place in the immediate postoperative period most likely because of a severely stenosed outflow tract.

Table 1 *Explanation of abbreviations used in the text*

FAP study	Direct femoral artery pressure study
GA Index at rest	Femoro-brachial systolic blood pressure index at rest
GA Index^{15}	GA Index after 15 s reactive hyperaemia
GA Index^{60}	GA Index after 60 s reactive hyperaemia
Index gradient = IG	The difference between GA Index at rest and GA Index^{15}
Return time index = RTI	The difference between GA Index at rest and GA Index^{60}

1. Flanigan D.P., Williams L.R., Schwartz J.A., Schuler J.J., Gray B.
Hemodynamic evaluation of the aorto-iliac system based on pharmacologic vasodilatation.
Surgery 1983, 93, 709-714.

2. Brewster D.C., Waltman A.C., O'Hara P.J., Darling R.C.
Femoral artery pressure measurements during aortography.
Circulation 1979, 60 (suppl. I): 120-124.

3. Brener B.J., Raines J.K., Darling R.C., Austen W.G.
Measurement of systolic femoral arterial pressure during reactive hyperemia; an estimate of aorto-iliac disease.
Circulation 1974, 49-50 (suppl. II): 259-266.

4. Flanigan D.P., Tullis J.P., Streeter V.L., Whitehouse W.M., Fry W.J., Stanley J.C.
Multiple subcritical arterial stenosis: Effect on poststenotic pressure and flow.
Ann. Surg. 1977; 186: 663-668.

5. Flanigan D.P., Gray B., Schuler J.J., Schwartz J.A., Post K.W.
Correlation of Doppler derived high thigh pressure and intra-arterial pressure in the assessment of aorto-iliac occlusive disease.
Br. J. Surg. 1981, 68: 423-425.

6. Brewster D.C., Perler B.A., Robison J.G., Darling R.C.
Aorta-femoral graft for multilevel occlusive disease. Predictors of succes and need for distal bypass.
Arch. Surch. 1982; 117: 1593-1600.

7. Haimovici H., Escher D.J.
Aorto-iliac stenosis; diagnostic significance of vascular hemodynamics.
Arch. Surg. 1956; 72: 107-117.

8. Weissman R.E., Upson J.F.
Intra-arterial pressure studies in patients with arterial insufficiency of the lower extremities.
Ann. Surg. 1963, 157, 501-506.

9. Wesolowski S.A., Martinez A., Domingo R.T. et al.
Indication for aorto-femoral arterial reconstruction. A study of borderline risk patients.
Surgery 1966, 60: 288-298.

10. Sako Y.
Papaverine test in peripheral arterial disease.
Surgical Forum 1966, 17: 141-143.

11. Moore W.S., Hall A.D.
Unrecognized aorto-iliac stenosis; a physiologic approach to the diagnosis.

Arch. Surg. 1971, 103: 633-638.

12. Lorentsen E., Hoel B.L., Hol R.
Evaluation of the functional importance of atherosclerotic obliterations in the aorto-iliac artery by pressure-flow measurements.
Acta Med. Scand. 1972, 191: 399-403.

13. Quin R.O., Evans D.H., Bell P.R.F.
Hemodynamic assessment of the aorto-iliac segment.
J. Cardiovasc. Surg. 1975, 16: 586-589.

14. Castaneda-Zuniga W., Knight L., Formanek A. et al.
Hemodynamic assessment of obstructive aorto-iliac disease.
Am. J. Roentgenol. 1976, 127: 559-561.

15. Bardach G.
Eine neue methode zur direktmessung des Aortofemoralen Druckgradienten im Rahmen der translumbalen Aortographie.
Fortschr. Geb. Röntgenstr. nuklearmed 1978, 128: 317-318.

16. Leveson S.H., Guillou P.J., Terry H.J., Glanville J.N., Kester R.C.
Pulse pressure wave analysis in the diagnosis of aorto-iliac disease.
Ann. Surg. 1978, 187: 161-165.

17. Udoff E.J., Barth K.H., Harrington D.P.
Hemodynamic significance of iliac artery stenosis: Pressure measurements during angiography.
Diagnostic Radiology 1979, 132: 289-293.

18. Evans D.H., Quin R.O., Bell P.R.F.
The significance of blood pressure measurement in patients with peripheral vascular disease.
Br. J. Surg. 1980, 67: 238-241.

19. Demorais D., Johnston K.W.
Assessment of aorto-iliac disease by non-invasive quantitative Doppler waveform analysis.
Br. J. Surg. 1981, 68: 789-792.

20. Verhagen P.F., van Vroonhoven Th.J.M.V.
Direct femoral artery pressure measurements at rest and during reactive hyperemia in the evaluation of the aorto-iliac segment.
J. Cardiovasc. Surg. 1984; 25: 395-399

21. Brewster D.C., Darling R.C.
Optimal methods of aorto-iliac reconstruction.
Surgery 1978, 84: 739-748.

22. Crawford E.S., Bomberger R.A., Glaeser D.H. et al.
Aorto-iliac occlusive disease: Factors influencing survival and function following reconstructive operation over a 25 year period.

Surgery 1981, 90: 1055-1067.

23. Moore W.S., Cafferata H.T., Hall A.D. et al.
In defense of grafts across the inguinal ligament: An evaluation of early and late results of aorto-femoral bypass grafts.
Ann. Surg. 1968, 168: 207-214.

24. Imparato A.M., Samoudos G., Epstein H.Y. et al
Results in 96 aorto-iliac reconstructive procedures: Preoperative angiographic and functional classifications used as prognostic guides.
Surgery 1970, 68: 610-616.

25. Perdue G.D., Long W.D., Smith R.B.
III: Perspective concerning aorto-femoral arterial reconstruction.
Ann. Surg. 1971, 173: 940-944.

26. Royster T.S., Lynn R., Mulcare R.J.
Combined aorto-iliac and femoro popliteal occlusive disease.
Surg. Gynecol. Obstet. 1976, 143: 949-952.

27. Edwards W.H., Wright R.S.
A technique for combined aorto-femoral-popliteal arterial reconstruction.
Ann. Surg. 1973, 179: 572-578.

28. Malone J.M., Moore W.S., Goldstone J.
The natural history of bilateral aorto-femoral bypassgrafts for ischemia of the lower extremities.
Arch. Surg. 1975, 110: 1300-1306.

29. Jones A.F., Kempczinski R.F.
Aorto-femoral bypass grafting: a reappraisal.
Arch. Surg. 1981, 116: 301-305.

30. Hill D.A., McGrath M.A., Lord R.S.A. et al.
The effect of superficial femoral artery occlusion on the outcome of aorto-femoral bypass for intermittent claudication.
Surgery 1980, 87: 133-136.

31. Martinez B.D., Hertzer N.R., Beven E.G.
Influence of distal arterial occlusive disease on prognosis following aorto-bifemoral bypass.
Surgery 1980, 88: 795-805.

32. Nevelsteen A., Suy R., Daenen W. et al.
Aorto-femoral grafting: Factors influencing late results.
Surgery 1980, 88: 642-653.

33. Baird R.J., Feldman P., Miles J.T. et al.
Subsequent downstream repair after aorto-iliac and aorto-femoral bypass operations.
Surgery 1977, 82: 785-793.

34. Mulcare R.J., Royster T.S., Lynn R.A. et al.
Long-term results of operative therapy for aorto-iliac disease.
Arch. Surg. 1978, 113: 601-604.

35. Benson R.J., Whelan T.J., Cohen A. et al.
Combined aorto-iliac and femoropopliteal occlusive disease: limitations of total aorto-femoro-popliteal bypass.
Ann. Surg. 1966, 163: 121-130.

36. Satiani B., Liapsis C.D., Evans W.E.
Aorto-femoral bypass for severe limb ischemia: Long-term survival and limb salvage.
Am. J. Surg. 1981, 141: 252-256.

37. Sumner D.S., Strandness D.E.
Aorto-iliac reconstruction in patients with combined iliac and superficial femoral arterial occlusions.
Surgery 1978, 84: 348-355.

38. Bone G.E., Hayes A.C., Slaymaker E.E., Barnes R.W.
Value of segmental limb blood pressure in predicting results of aorto-femoral bypass.
Am. J. Surg. 1976, 132: 733-738.

39. Bruins-Slot H., Strijbosch L., Greep J.M.
Intraobserver variability in single-plane aortography.
Surgery 1981, 90: 497-503.

40. Nicolaides A.N., Gordon-Smith I.C., Dayandas F.R., Eastcott H.H.G.
The value of Doppler blood velocity tracings in the detection of aorto-iliac disease in patients with intermittent claudication.
Surgery 1976, 80: 774-778.

41. Faris I.B., Jamieson C.W.
The diagnosis of aorto-iliac stenosis. A comparison of thigh pressure measurements and femoral artery flow velocity profile.
J. Cardiovasc. Surg. 1975, 16: 597-602.

42. Baird R.N., Bird D.R., Clifford P.C., Lusby R.J., Skidmore R., Woodcock J.P.
Upstream stenosis: Its diagnosis by Doppler signals from the femoral artery.
Arch. Surg. 1980, 115: 1316-1322.

43. Harris P.L., Taylor L.A., Cave F.D., Charlesworth D.
The relationship between Doppler ultrasound assessment and angiography in occlusive arterial disease of the lower limbs.
Surg. Gynecol. Obstet. 1974, 138: 911-914.

44. Archie J.P., Feldtman R.W.
Determination of the hemodynamic significance of iliac artery stenosis by non-invasive Doppler ultra sonography.

Surgery 1982, 91: 419-424.

45. Heintz S.E., Bone G.E., Slaymaker E.E., Hayes A.C., Barnes R.W.
Value of arterial pressure measurements in the proximal and distal part of the thigh in arterial occlusive disease.
Surg. Gynecol. Obstet. 1978, 146: 337.

46. Johnston K.W., Taraschuk I.
Validation of the role of pulsatility index in quantitation of the severity of peripheral arterial occlusive disease.
Am. J. Surg. 1976, 131: 295-297.

47. Ward A.S., Martin T.P.
Some aspects of ultrasound in the diagnosis and assessment of aorto-iliac disease.
Am. J. Surg. 1980, 140: 260-265.

48. O'Donnell T.F., Lahey S.J., Kelly J.J. et al.
A prospective study of Doppler pressures and segmental plethysmography before and following aorto-femoral bypass.
Surgery 1979, 86: 120-128.

49. Johnston K.W.
Systolic slope and other pressure measurements in patients with peripheral vascular disease.
Surg. Gynecol. Obstet. 1975, 140: 249-251.

50. Hurlow R.A., Chandler S.T., Hardman J., Strachan C.J.L.
The non-invasive assessment of aorto-iliac disease: A comparison of dynamic isotope angiology with thigh/brachial pressure index.
Surgery 1978, 84: 278.

51. Cranley J.J., Hafner C.D.
Revascularisation of the femoro-popliteal arteries using saphenous vein, polytetrafluoroethylene and umbilical vein grafts.
Arch. Surg. 1982, 117: 1543-1550.

CHAPTER X

CONCLUSIONS AND RECOMMENDATIONS

X.1 Introduction

The aim of this study was to develop a simple, reliable and inexpensive means of investigating patients with symptoms suggestive of arterial obstructive disease of the lower extremities.
Following a review of the relevant literature on the subject (chapters II, III and IV), a study was performed. The study was planned on conclusions drawn from the literature review.
The method used in this study was the measurement of blood pressure at rest and during post-ischemic reactive hyperemia.
Direct (intra-arterial) blood pressure measurements were taken at femoral level and indirect measurements were taken at the ankle (chapters V, VI, VII, VIII, IX).

X.2 Conclusions

In chapter II, some aspects of the hemodynamics of the arterial circulation in health and disease states are described.
It is concluded that Poiseuille's Law can define only the minimal energy loss of moving blood that can be expected under any given blood flow condition, since this Law requires circumstances which are never fully met in the (patho)physiologic situation.
Poiseuille's Law describes the viscous energy loss of moving fluid between two points of a tube.
For the Law to hold, the tube must be non-compliant, the fluid newtonian in its behaviour and the flow laminar and non-pulsatile. The energy loss is then mainly dependent on the cross-sectional area of the tube. However, a stenosis in a blood vessel has a critical degree of narrowing, beyond which any increase in the narrowing produces a fall in blood pressure and -flow downstream, greater than that predicted by Poiseuille's Law.
The higher the blood flow velocity through the stenosis, the less is the degree of narrowing needed to reach this critical point.
Inertial energy loss is directly proportional to the square of flow velocity. Experimentally, this inertial energy loss has been shown to be greater and hence more important than viscous energy loss.
The conclusion seems justified that a diagnostic test should be performed during high flow states, since intermittent claudication arises during periods of increased blood flow velocity induced by muscular exercise.
In chapter III, the currently used methods of diagnosing and investigating peripheral arterial obstructive disease are described.
Blood flow measurements at the calf level and pressure measurements at the ankle level, are sufficient to determine whether arterial insufficiency is present, and if so, to what degree. Blood flow measurements need to be taken during hyperemia to be of value. In contrast, blood pressure measurements taken at rest provide much

information. Because of the simplicity of taking blood pressure measurements at the ankle using Doppler ultrasonography, we decided to employ this technique instead of blood flow measurements for our study.
The question as to whether blood pressure measurements at rest are as informative as during PIRH has been addressed in chapter VII.
Symptoms due to arterial insufficiency are very often caused by obstructions at different levels of the arterial tree.
From a therapeutic viewpoint the assessment of the aorto-iliac segment is very important, as the result determines whether a proximal or a distal vascular reconstruction need be performed.
There are several diagnostic methods available to localize arterial obstructions.
Table 1 in chapter III summarizes these methods and their results, expressed in statistical indices as they were obtained by different authors.
It is important to realize that parameter-thresholds, goldstandards and patient populations varied between the different studies, so comparison should be made with caution.
Femoral pulse palpation and angiography (even triplane angiography), when used as the only diagnostic methods, are insufficient to assess the hemodynamic significance of aorto-iliac disease.
The results obtained with thigh pressure measurements are controversial.
The advantages of this method are in its simplicity and non-invasive character.
Thigh pressure measurements compare poorly with direct femoral artery pressure measurements (ref. 5 chapter IX).
This is of obvious importance, as direct femoral artery pressure measurements are probably the best means of assessing obstructive disease of the aorto-iliac segment (ref. 12-29, chapter VIII).
Flanigan et al used a wide thigh cuff in the above-mentioned study.
Heintz et al (ref.45, chapter IX) reported improved results with the use of a narrow cuff and claimed even better results with a combination of narrow high- and low thigh cuffs. However, angiography was used as the goldstandard in this study.
Combinations of thigh pressure measurements with another method (Bruyninckx '76: thigh pressure and ankle pressure, Buth '78: thigh pressure and pulse volume recording, Kitslaar '82 and Fronek et al '78: thigh pressure and Doppler waveform analysis of the femoral blood flow velocity signal, chapter III) gave reasonable to good results.
Angiography was also used as the goldstandard in these studies.
The greatest drawback of thigh pressure measurements is that femoro-popliteal disease influences the result (page 482 ref. 25, chapter III).
Thus the method is unreliable when multiple level disease exists.
The analysis of the Doppler derived, blood flow velocity waveform of the common femoral artery is another non-invasive method of assessing the aorto-iliac segment.
In chapter III the different techniques of analyzing the blood flow velocity waveform are described.
The results of qualitative and semi-quantitative analysis of the

Doppler velocity waveform in assessing the aorto-iliac segment are controversial.
Flanigan et al (ref. 81, chapter III) showed that the results of Doppler waveform analysis correlate poorly with common femoral intra-arterial pressure measurements. Faris and Jamieson (ref. 30, chapter III) reported a high percentage of borderline and abnormal velocity waveforms (45%) in patients with isolated superficial femoral disease.
Like thigh pressure measurements, the blood flow velocity waveform of the common femoral artery is influenced by both inflow and outflow disease.
The Pulsatility Index (P.I.), a parameter calculated from the velocity waveform, has the same limitation. The P.I., calculated preferably from the spectrum analyzed frequency envelope of the Doppler signal, was found to correlate well with angiographic gradings by Johnston et al in various studies (ref. 72-74, chapter III) and by Harris et al (ref. 71, chapter III). However, Baird et al (ref. 77, chapter III), Ward and Martin (ref. 76, chapter III), and Flanigan et al (ref. 82, chapter III) reported that the P.I. has limited value in the presence of superficial femoral arterial disease, in the assessment of the aorto-iliac segment. Baird et al found a sensitivity of only 41%.
The L.T. Factor (Laplace Transform Analysis Factor), a mathematical expression of the velocity waveform, seems to be more promising in multiple level disease (ref. 77, 78, chapter III).
Unfortunately sophisticated and expensive equipment is required for the analysis of the Doppler signal.
Many studies conclude (ref. 80 and table 1, chapter III and ref. 12-29, chapter VIII) that direct femoral artery pressure measurement, expecially when performed during hyperemia, is the best method of assessing the aorto-iliac segment.
One disadvantage is that it is an invasive technique. It can, however, be readily combined with angiography, and many authors have reported on the safety and efficacy of this combination (ref. 1,3-6, 8, 19, 20 in Flanigan et al, 1984, ref. 80, chapter III). Femoro-popliteal disease has little or no influence on the measurements obtained (ref. 3, chapter IX) and the equipment required is inexpensive and uncomplicated.
Because of these considerations, it was decided to use and test this method in combination with PIRH, to assess the aorto-iliac segment in multiple level disease (chapter VIII and IX) and to establish parameter-thresholds for significant aorto-iliac disease.
In chapter IV, the three most commonly used methods of creating a high flow state are described: Post-exercise hyperemia (PERH), Post-ischemic hyperemia (PIRH) and pharmalogically induced hyperemia (PRH).
Each of these methods induce similar, maximal increases in peripheral blood flow and similar maximal decreases in peripheral blood pressure, in patients with equivalent degrees of arterial obstructive disease.
The PRH method is a simple procedure, which induces a blood flow increase comparable to that induced by moderate exercise. It requires, however, the intra-arterial injection of a pharmacological agent which may be accompanied by undesirable side effects.

Papaverine is most commonly used.
The PERH method, using a standardized amount of exercise, is the most physiological way of inducing blood flow changes. Coexistent physical illness and other factors, such as walking technique, training, body weight and patient cooperation may influence the amount of exercise performed.
Furthermore, Hylkema (ref. 9, chapter IV) was unable to find a correlation between the anamnestic claudication time and the relative treadmill claudication time (time to the onset of pain).
It is therefore not surprising, that the reproducibility of the treadmill test is not very good (ref. 18,19, chapter IV, ref. 10 chapter VII).
However, the response of blood flow or blood pressure is reported to correlate approximately with the angiographic extent of arterial obstructive disease (ref. 28, 29, 30 chapter IV).
The PIRH test seems to be an attractive alternative. The maximal reaction of blood flow and blood pressure is similar to the maximal reaction observed after moderate exercise but the subsidence of the PIRH reaction takes a shorter period than that of the PERH reaction. The test requires little patient cooperation and may accordingly be more reproducible than a PERH test. (ref. 26, 76, 80, 81, chapter IV).
A disadvantage of a PIRH test is that one does not observe the patient exercising.
Another practical point is that in healthy persons a very short lasting blood pressure drop can be observed during PIRH, immediately after the restoration of arterial inflow. This pressure drop is always less than in patients with arterial obstructive disease. (ref. 79, 82, chapter IV).
Because of technical difficulties in the recording of the blood pressure immediately after exercise, the first measurement is usually obtained 30 to 60 seconds after the cessation of exercise. After this 30 to 60 seconds interval, it is a rare occurrence to record a blood pressure drop in healthy persons after moderate exercise but a brief drop is occasionally recorded after strenuous exercise (ref. 79, chapter IV).
It is possible, of course, that blood pressure falls in all persons in the immediate post-exercise period, but escapes detection because of the pause before the first measurement.
After intra-arterial papaverine, a transient blood pressure drop can be observed to a maximum of $6\% \pm 5\%$ in persons with $\leq 30\%$ stenoses in the aorto-iliac segment (ref. 78,79, chapter III).
Chapters V and VI detail the results of a comparative study of systolic ankle blood pressure measurements during PIRH and PERH (the treadmill test).
The purpose of this study was to determine the most useful method.
The ankle pressure results of the PIRH test were comparable to the ankle pressure results of the PERH test.
The correlation between the maximal blood pressure response of both tests, was excellent.
This maximal response is diagnostically the most valuable parameter, as was shown in chapter VII.
The PIRH test was decided upon as being of the most use as it has

several advantages over the PERH test. The PIRH test is likely to be more reproducible, as it does not require as much patient cooperation. It takes less time and space to perform and can be done on patients who cannot manage the treadmill or who are disabled by cardio-pulmonary diseases.
The PIRH test can also be performed intraoperatively or in the immediate postoperative period.
A theoretical contraindication to the use of the PIRH test is the presence of a patent femoro-popliteal bypass. There is no evidence in the literature to date to support such a conjecture.
With the PIRH test, one does not obtain objective evidence of the patient's exercise tolerance. The treadmill walking time has, however, proven to be of little diagnostic value (chapter IV 2.2. and ref. 10, chapter VII).
Chapters VI and VII describe three clinical studies.
Firstly, the value of four parameters in assessing the clinical severity of arterial obstructive disease was evaluated. These four parameters were: the systolic ankle-arm pressure index at rest, the minimal index during PIRH (15 second index), the difference between the index at rest and the 15 second index (I.G.) and the recovery time of the ankle-arm index (R.T.). Secondly, the efficacy of these four parameters in localizing hemodynamically significant lesions was determined.
The diagnosis of a hemodynamically significant lesion was based on angiography.
Finally, the reproducibility of the PIRH test was investigated in chapter VI.
The conclusion, that the PIRH test has good reproducibility has been confirmed by others (ref. 26, 76, 80, 81, chapter IV).
Ouriel et al (ref. 10, chapter VII), comparing resting, post-exercise and post-ischemic ankle pressures, concluded that the resting ankle index is the most reproducible parameter (relative standard deviation, R.S.D. 9.5%), walking distance was found least reproducible (R.S.D. 43.9%). Post-exercise and post-ischemic minimal indices were equally reproducible parameters (R.S.D. $\pm$ 15%).
In our study, the value of systolic ankle-arm pressure indices at rest, was as good as three parameters derived from ankle pressure measurements during PIRH in determining the degree of arterial obstructive disease, or in localizing the hemodynamically significant lesions.
Although many authors (ref. 1-9, chapter VII) advise performing blood pressure measurements during hyperemia as well as in rest, it is concluded from this and several other studies (ref. 10, chapter VII, and ref. 1, 2, 35, chapter III), that the routine measurement of blood pressure during hyperemia is unnecessary.
Resting systolic blood pressure measurements at the ankle are generally sufficient to determine the existence of and the severity of arterial obstructive disease.
This statement may not hold true for patients with asymptomatic, mild degrees of atherosclerosis.
It is concluded from this study that in only a few clinical situations, it is useful to perform additional pressure measurements

at the ankle during hyperemia.
On the rare occasion when a patient has a definite history of intermittent claudication and an ankle-arm index at rest of > 100%, it is advisable to perform a test during hyperemia (ref. 5, chapter VII).
Another indication occurs when signs of multiple level disease are detected during physical examination. If the minimal index during PIRH is then < 20%, there is a good chance that multiple level disease is present. It is then advisable to add a test with enough sensitivity to detect hemodynamically significant aorto-iliac disease (fig. II, chapter VII). We decided upon direct femoral artery pressure measurements at rest and during PIRH (FAP study) to assess the aorto-iliac segment in multiple level disease.
Chapter VIII contains the results of our first experiences with this method.
The study started with a retrospective correlation between the 6 month postoperative results of 38 vascular reconstructions and the preoperative FAP results.
In each case the decision to perform a distal or proximal reconstruction was made by experienced vascular surgeons, based on history, physical examination, ankle blood pressures and single plane angiography, the FAP results did not play a role in the decision making.
The angiograms showed multilevel arterial obstructive disease. A stenosis was considered hemodynamically significant, when the percentage diameter reduction of the arterial lumen exceeded 50% (this corresponds to a 70-75% cross-sectional area reduction).
Categorization of a patient into the improved group, required a history of clearly improved walking distance and an increase in ankle-arm blood pressure index of at least 10%.
As discriminant values for significant aorto-iliac disease we selected:
-a- a femoral-arm systolic pressure index at rest of < 70% (GA index at rest < 70%).
-b- an Index Gradient (difference between GA index at rest and minimal index during PIRH) of > 20%, if the GA index at rest is > 70%.
The values were chosen because of our experience with the method and based on certain hemodynamic principles.
It is more scientific to obtain a discriminant value from a receiver-operator characteristic curve analysis (ROC analysis).
In a ROC analysis, sensitivities and specificities of different discriminant values are plotted. The ROC curve provides a dynamic relationship between sensitivity and specificity, compared to a specific standard of evaluation.
At a later stage, our data were analyzed by means of a ROC curve. (Fig. I)

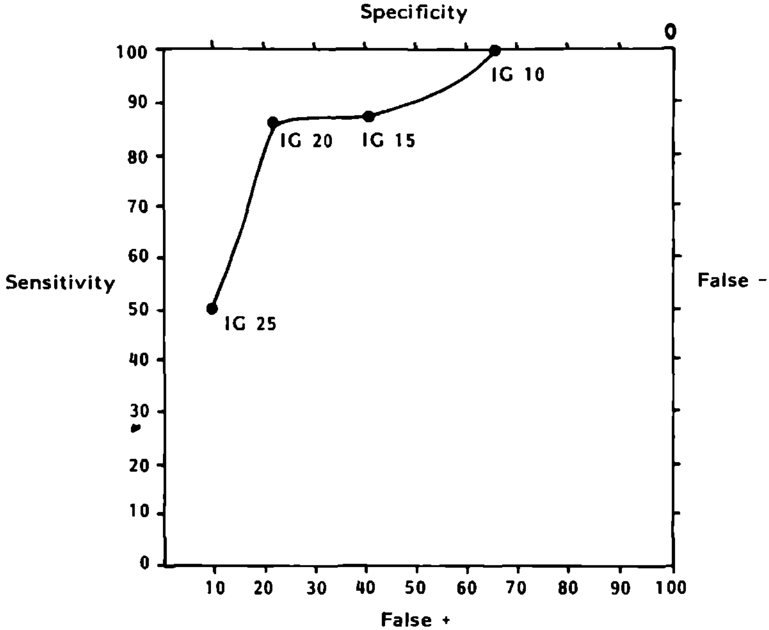

Figure 1. Receiver operator characteristic curve of the index gradient (IG) in the assessment of the aorto-iliac segment. Gold standard is the hemodynamic result of a vascular reconstruction.

As can be seen in figure I, the curve is smoothly shaped with the apex high in the left upper corner of the graph (the point of highest sensitivity and specificity). A threshold I.G. of 20 proves to be of better discriminatory value than 10, 15 or 25. When one of the FAP criteria for significant aorto-iliac disease was positive, 70% (7/10) of the proximal reconstructions resulted in hemodynamic improvement. When the FAP criteria were negative, 91% (11/12) of the proximal reconstructions resulted in no improvement. Following distal reconstructions, there was improvement in 84% (11/13) of limbs with negative FAP criteria. In relation to the results of proximal

reconstructions, the FAP criteria were found to have a sensitivity of 87%, a specificity of 78% and an accuracy of 81%. The positive predictive value (PPV) was 70% and the negative predictive value (NPV) 91%, in determining the presence of significant aorto-iliac disease.
In correlation with postoperative symptomatology of patients who underwent either a proximal or a distal reconstruction, angiography had an 80% sensitivity, 50% specificity and 58% accuracy in predicting a satisfactory outcome. The PPV was 36% and the NPV 87%.
The assessment of the hemodynamic significance of aorto-iliac disease from angiography is compared with the FAP studies in the latter part of chapter VIII. In predicting significant disease with the FAP study results as the goldstandard, angiography had only 50% sensitivity, 80% specificity and 76% accuracy. The PPV was 30% and the NPV 90%. The low PPV's indicate that angiography, in identifying significant aorto-iliac disease, is likely to be incorrect in about 65% to 70% of cases, using the FAP studies or post-operative course as goldstandards.
Similarly, the high NPV's indicate that the absence of significant disease at angiography will be in agreement with the standards in most cases.
Chapter IX outlines the prospective use of the FAP criteria.
Fourty-five patients underwent a proximal (n=22) or a distal (n=23) vascular reconstruction, as dictated by FAP results, except for 8 patients with associated, aorto-iliac, aneurysmal disease.
Angiograms revealed multiple level disease in each case. The FAP criteria were evaluated using the 6 month clinical result of the reconstructions as the goldstandard.
In 19 extremities, a positive FAP criterion indicated the presence of significant aorto-iliac disease. All these extremities improved after a proximal reconstruction.
In 23 extremities the FAP criteria were negative. Twenty had a satisfactory crural run-off and were improved by a distal reconstruction.
The three extremities with poor crural run-off developed an occlusion of the distal reconstruction in the immediate postoperative period.
Further vascular surgery was considered to offer no benefit and reexploration was not performed.
Two of these distal reconstructions were femoro-crural bypasses for limb salvage.
Eight extremities had negative FAP criteria but associated aneurysmal disease of the aorto-iliac segment. Because of the aneurysmal disease a proximal reconstruction was then performed in each, with no hemodynamical improvement in five.
Omitting these eight proximal reconstructions, which were performed contrary to the FAP criteria recommendations, and the three distal reconstructions that occluded in the immediate postoperative period mainly because of crural obstruction, produces impressive results. The FAP criteria have then 100% accuracy, 100% specificity and 100% sensitivity in diagnosing hemodynamically significant aorto-iliac disease. The PPV and NPV are both 100% too.
Omitting only the three occluded distal reconstructions from calculations, produces a 93% accuracy, 86% sensitivity and 100%

specificity.
The PPV is 100% and the NPV 89%.
Including all patients, the FAP test has an 88% accuracy, 76% sensitivity and 100% specificity.
The PPV is 100% and the NPV is 80%.
The results of a similar, prospective study were recently published. Flanigan et al (ref. 80, chapter III) used FAP studies combined with intra-arterial papaverine injections to assess the aorto-iliac segment and compared these results to the post-operative clinical course. Simultaneous blood flow velocity measurements over the common femoral artery identified the point of maximal velocity increase and blood pressure measurements were performed at this point.
They used a similar discriminant value (%ΔFBI$\geq$ 15%) and found a 94% sensitivity, 100% specificity and 98% accuracy in predicting an improvement after vascular reconstruction in multiple level disease. The PPV was 100% and the NPV 98%.
Both prospective FAP studies have thus achieved excellent results in the assessment of the aorto-iliac segment in multiple level arterial obstructive disease of the lower extremities.
PIRH or intra-arterial papaverine seem to have a similar efficacy in creating a high flow state.
The choice is then a matter of personal preference.

X.3 Recommendations

Following our research and investigations, we have developed a management protocol for patients presenting with symptoms suggestive of arterial obstructive disease of the lower extremities.
We have found this protocol simple and effective.
In patients with a history and physical examination suggestive of arterial obstructive disease, our first step is the measurement of the systolic ankle-arm pressure index at rest by Doppler ultrasonography.
If this index exceeds 100%, but clinically the presence of arterial obstructive disease is suspected, the ankle blood pressures are measured during PIRH.
If the difference between the index at rest and the lowest index during PIRH (the Index Gradient) is less than 20%, there is little chance that the complaints of the patient are due to arterial obstructive disease (see Fig. I, chapter VII).
If the Index Gradient exceeds 20%, it is possible that ischemia exists only during exercise.
With an ankle-arm pressure index at rest less than 100%, arterial obstructive disease is present.
The lower the rest index, the more severe are the obstructions.
Angiography can then be performed in those with positive ankle pressure measurement results.
The presence of multiple level disease of hemodynamic importance can be suggested by a 15 second index of the PIRH test less than 20% or by angiographic appearances.
An FAP study at rest and during PIRH should then be performed.
When the GA index at rest (GA index = femoro-brachial pressure index) is less than 70%, additional pressure measurements during PIRH are unnecessary, as the index indicates almost total occlusion of the upstream vessel (ref. 7, chapter IX). A proximal reconstruction is then indicated.
Additional blood pressure measurements during PIRH are needed, when the GA index at rest exceeds 70%.
A proximal reconstruction is indicated when the Index Gradient of the FAP test exceeds 20%. This Index Gradient is the difference between the resting GA index and the minimal GA index during PIRH.
A distal reconstruction is indicated, when the Index Gradient is less than 20%.
When the Index Gradient of the FAP study exceeds 20% or the GA index at rest is less than 70%, a proximal reconstruction should improve or abolish symptoms in virtually all patients with multiple level disease.
A femoro-politeal bypass will be succesful hemodynamically and have a high patency rate during the first 6 months, in patients with angiographic multiple level disease, when the crural outflow is satisfactory and the Index Gradient of the FAP test is less than 20%.

POST-ISCHEMISCHE REACTIEVE HYPEREMIE IN DE DIAGNOSE VAN HET PERIFEER ARTERIEEL VAATLIJDEN.

Het doel van deze studie was het ontwikkelen van een simpel en betrouwbaar onderzoeksschema voor patienten met symptomen, suggestief voor een obstruerend arterieel vaatlijden van de onderste extremiteiten.
De vraagstellingen waren:
1. Is obstruerend arterieel vaatlijden de oorzaak van de klachten van de patient en zo ja, kan de ernst van het vaatlijden in een objectieve maat worden weergegeven?
2. Wat is de beste manier om bij meer etage afwijkingen in het vaatstelsel van bekken en benen, de hemodynamisch meest belangrijke afwijkingen te lokaliseren?
In de hoofdstukken II, III en IV wordt een overzicht van de relevante literatuur gegeven.
In hoofdstuk II worden enkele fundamentele aspecten betreffende hemodynamiek en (patho-)fysiologie van het vaatstelsel besproken.
In hoofdstuk III worden de verschillende mogelijkheden in het onderzoek van het arteriele vaatstelsel van de onderste extremiteiten en de resultaten van deze methoden beschreven.
Op grond van de conclusies uit hoofdstuk II lijkt onderzoek tijdens verhoogde bloedstroomsnelheid noodzakelijk om de eerder genoemde vraagstellingen te kunnen beantwoorden. Tijdens reactive hyperemie bestaat een verhoogde bloedstroomsnelheid door verlaging van de perifere vaatweerstand.
In hoofdstuk IV worden, derhalve, de drie meest toegepaste manieren om reactieve hyperemie op te wekken, beschreven. Bovendien worden de voor- en nadelen van de verschillende methoden besproken.
De hoofdstukken V, VI, VII, VIII en IX omvatten het eigen onderzoeksgedeelte.
De hoofdstukken V, VI en VII betreffen voornamelijk de le vraagstelling. De hoofdstukken VIII en IX en gedeeltelijk hoofdstuk VII hebben betrekking op de 2e vraagstelling.
In hoofdstuk V wordt een vergelijkend onderzoek beschreven tussen 2 functionele testen bij patienten en gezonde personen. Functioneel betekent dat bij beide testen tijdens reactieve hyperemie metingen worden uitgevoerd. In de ene test worden enkelbloeddrukken gemeten nadat de patient inspanning heeft verricht op een tredmolen (PERH test). Bij de andere test worden de enkelbloeddrukken gemeten tijdens post-ischemische reactieve hyperemie (PIRH test). De conclusie van deze studie is dat er een goede correlatie tussen de uitkomsten van beide testen bestaat. Op grond van een aantal factoren, wordt de voorkeur gegeven aan de PIRH test.
Hoofdstuk VI bevat een onderzoek naar de reproduceerbaarheid van de

PIRH test en naar de waarde van de PIRH test in de diagnostiek van het perifeer arterieel vaatlijden.
De conclusie is dat de reproduceerbaarheid van de PIRH test redelijk is. De diagnostische waarde van 3 parameters ontleend aan de PIRH test werd nagegaan in 4 groepen patienten die op grond van de ernst van het klinisch beeld waren ingedeeld. De conclusie is dat géén van deze 3 parameters op zich, meer informatie oplevert dan de systolisch enkel-arm bloeddruk index in rust.
In hoofdstuk VII wordt de waarde van de eerder genoemde 3 parameters ten aanzien van de localisatie van hemodynamisch belangrijke afwijkingen in het vaatstelsel van de onderste extremiteiten nagegaan. De PIRH test werd daartoe uitgevoerd bij 3 groepen patienten die op basis van een bekken-benen angiogram waren verdeeld in een groep met alleen aorto-iliacale afwijkingen, een groep met alleen femoro-popliteale afwijkingen en een groep met meer-etage afwijkingen. Ook in dit geval blijkt de waarde van de enkel-arm bloeddruk index in rust niet onder te doen voor de PIRH parameters.
Aan de hand van een uitgebreid literatuur overzicht en aan de hand van de eigen resultaten, wordt in hoofdstuk VII getracht om tot een indicatie stelling voor bloeddruk onderzoek aan de enkel tijdens hyperemie te komen. Onze conclusie is dat het routinematig uitvoeren van bloeddruk onderzoek aan de enkel tijdens hyperemie niet is aangewezen, daar onderzoek in rust goed in staat is om de ernst van het arterieel vaatlijden aan te tonen. Deze conclusie geldt alleen voor patienten die zich met klachten, mogelijk berustend op arteriele insufficientie van de onderste extremiteiten, aandienen, daar het onderzoek bij een dergelijke groep patienten is uitgevoerd.
Bloeddruk-onderzoek aan de enkel, of dit nu in rust dan wel tijdens hyperemie wordt uitgevoerd, is niet het onderzoek van keus indien men de localisatie van hemodynamisch belangrijke afwijkingen in het vaatstelsel van de onderste extremiteiten wil aantonen. Op grond van literatuur onderzoek en uitgaande van onze doelstelling is, ter localisatie van hemodynamisch belangrijke afwijkingen, gekozen voor directe bloeddrukmeting in de arteria femoralis communis in rust en tijdens PIRH (de FAP test).
In hoofdstuk VIII worden de eerste ervaringen met de FAP test, in een retrospectief onderzoek bij patienten met aorto-iliacale afwijkingen op het angiogram, beschreven. Op basis van literatuurgegevens en eigen ervaring met de FAP test, werden criteria opgesteld voor het aanwezig zijn van hemodynamisch belangrijke afwijkingen in het aorto-iliacale traject. In een latere fase (zie hoofdstuk X) werd de juiste keus van deze criteria bevestigd aan de hand van een "receiver operator characteristic curve" analyse. Als criteria voor hemodynamisch belangrijke afwijkingen in het aorto-iliacaal traject werden gehanteerd:
a. een lies-arm bloeddrukindex in rust (GA index in rust) van < 70%.
b. een Index Gradient (verschil tussen GA index in rust en laagste GA index tijdens PIRH) van > 20%, indien de GA index in rust > 70% is.
Angiografie bleek ter bepaling van hemodynamisch belangrijke afwijkingen in het aorto-iliacaal traject 80% sensitief, 50% specifiek en 58% accuraat te zijn indien het resultaat van een vasculaire reconstructie, een half jaar postoperatief, als goudstandaard werd

gehanteerd.
De positive predictive value (PPV) was in dat geval 36% en de negative predictive value (NPV) 87%. Indien de FAP criteria als goudstandaard gebruikt werden, bleek angiografie 50% sensitief, 80% specifiek en 76% accuraat. De PPV was dan 30% en de NPV 90%. Met name de lage waarden van de PPV in beide correlaties, wijzen erop dat men de neiging heeft het hemodynamisch belang van afwijkingen in het aorto-iliacaal traject te overschatten.
Wanneer de FAP criteria werden gecorreleerd met het postoperatief resultaat van proximale reconstructies dan bleek dat de FAP criteria 87% sensitief, 78% specifiek en 81% accuraat waren. De PPV was in dat geval 70% en de NPV 91%.
De conclusie is dat op basis van de preoperatief verkregen FAP criteria het functionele resultaat van een vasculaire reconstructie in het aorto-iliacaal traject waarschijnlijk beter kan worden beoordeeld dan alleen op basis van de beoordeling van het angiogram. Derhalve werd besloten deze FAP criteria te onderzoeken in een prospectieve studie.
In hoofdstuk IX worden de resultaten beschreven van dit prospectieve onderzoek. Bij 45 symptomatische patienten met meer-etage afwijkingen op het angiogram werd op basis van de FAP criteria gekozen voor een proximale dan wel distale vasculaire reconstructie. Het postoperatieve resultaat na een half jaar werd als goudstandaard gebruikt in de correlatie met de FAP criteria.
De conclusie van dit onderzoek is dat de FAP criteria 100% sensitief, 100% specifiek en 100% accuraat zijn in de voorspelling van het functionele resultaat van een vasculaire reconstrutie bij meer-etage afwijkingen. De PPV is 100% en de NPV is eveneens 100%. Bij deze resultaten dient een kanttekening te worden geplaatst. Drie distale reconstructies tromboseerden in de direct postoperatieve fase. Zij zijn in de berekeningen van bovengenoemde resultaten niet verdisconteerd, omdat in alle 3 gevallen een zeer slechte crurale "outflow" bestond. De indruk bestond derhalve dat niet een belemmerde aorto-iliacale "inflow" doch een slechte crurale "outflow" de oorzaak van de trombosering was. Acht extremiteiten vertoonden angiografisch bijkomende aneurysmatische afwijkingen in het aorto-iliacaal traject. In weerwil van de negatieve FAP criteria werd in deze 8 gevallen toch een proximale reconstructie verricht. In 5 gevallen verbeterde de hemodynamische toestand van de extremiteit, zoals werd verwacht, niet. In 3 werd echter wel hemodynamische verbetering vastgesteld. Ook deze 8 gevallen werden niet in de bovengenoemde berekening opgenomen; omdat ze niet op grond van de FAP criteria in de proximale reconstructie groep waren opgenomen.
Indien echter deze 11 bijzondere gevallen in de berekeningen worden meegenomen, dan is de sensitiviteit 76%, de specificiteit 100% en de accuratesse 88%. De PPV is in dat geval 100% en de NPV 80%.
De conclusie van de prospectieve studie is dat de FAP test een eenvoudige en zeer betrouwbare methode is om het resultaat van een vasculaire reconstructie bij meer-etage afwijkingen te voorspellen. De FAP criteria, zoals die zijn gehanteerd, blijken zeer geschikt te zijn om het hemodynamisch belang van afwijkingen, zichtbaar op een aorto-iliacaal angiogram, te objectiveren.

De FAP test heeft als nadeel dat het een invasieve methode is doch het onderzoek kan zeer eenvoudig gecombineerd worden met conventionele angiografie waardoor dit nadeel grotendeels vervalt.

SUMMARY

POST-ISCHEMIC REACTIVE HYPEREMIA IN THE DIAGNOSIS OF PERIPHERAL ARTERIAL OBSTRUCTIVE DISEASE.

The aim of this study was to develop simple and reliable means of investigating patients with symptoms suggestive of arterial obstructive disease of the lower extremities.
The following questions were addressed:
1. Is it possible to assess objectively the presence and severity of the arterial obstructive disease?
2. What is the best method for localizing the hemodynamically, most significant lesions in the presence of multiple-level arterial obstructive disease?
Chapters II, III and IV contain a review of the relevant literature. Chapter II deals with the basic aspects of hemodynamics and the (patho-)physiology of the arterial tree.
In chapter III the various methods used for investigating a patient with arterial obstructive disease and their results are described. Based on the conclusions of chapter II, it seems that a diagnostic test needs to be performed during increased blood flow velocity i.e. during hyperemia, to answer the abovementioned questions. During reactive hyperemia, increased blood flow velocity is created by lowering the peripheral vascular resistance.
In chapter IV, the three most commonly used methods of inducing reactive hyperemia and their advantages and disadvantages are discussed.
Chapters V, VI, VII, VIII and IX contain the descriptions and results of our own study. Chapters V, VI and in part VII cover the detection of and the assessment of peripheral vascular disease.
Chapters VII, VIII and IX deal with the localization of hemodynamically significant lesions in the presence of multiple-level disease.
In chapter V a comparative study between two tests is described. In one test, systolic ankle pressures during postexercise reactive hyperemia (PERH test) were measured. In the other test ankle pressures were measured during postischemic reactive hyperemia (PIRH test).
The conclusion of this study was that a good correlation exists between the maximal ankle blood pressure responses induced by each test. Based on several factors, outlined in the text, we decided to use the PIRH test for further study.
Chapter VI contains a reproducibility study of the PIRH test and an assessment of its value in the diagnosis of arterial obstructive disease. The conclusion was that the PIRH test has a reasonable level of reproducibility.
The diagnostic value of three parameters derived from the PIRH test, was assessed in four groups of patients, classified on clinical grounds. None of these three parameters were found to be of more diagnostic value than the systolic ankle-arm pressure index at rest alone.
Chapter VII contains an assessment of the value of the three PIRH

parameters in the localization of the hemodynamically, most significant lesions.
Three groups of patients were divided according to the results of angiography into those with aorto-iliac disease alone, those with femoro-popliteal disease alone, and into those with multiple-level lesions. Each group underwent the PIRH test. The diagnostic value of the three PIRH parameters again were not found to be better than that of the ankle-arm pressure index at rest.
Based on a literature review and on our own results, we attempted to define the indications for blood pressure measurements at the ankle during reactive hyperemia.
The reasoning is described in chapter VII. The conclusion was that the routine measurement of ankle pressure during hyperemia is not necessary, since ankle pressure measurements at rest give a satisfactory assessment of the severity of arterial obstructive disease.
This conclusion only holds true for symptomatic patients. Furthermore, ankle pressure measurement, either at rest or during reactive hyperemia, is not the method of choice to localize the hemodynamically, significant lesions in the vascular tree of the lower extremities.
Based on the literature review, we decided that intrafemoral blood pressure measurements at rest and during reactive hyperemia (FAP test) were of most value in assessing the hemodynamic significance of the aorto-iliac segment in multiple-level disease.
In chapter VIII the first experiences with the FAP test are described in a retrospective study of patients with evidence of arterial obstructive disease on aorto-iliac angiography.
Based on our experience with the FAP test and on a receiver operator characteristic curve analysis of different discriminant values (chapter X), the best criteria for the presence of hemodynamically, significant, aorto-iliac disease were determined.
The criteria are: 1. a groin-arm systolic blood pressure index at rest (GA index at rest) of less than 70%, or 2. an Index Gradient (difference between G-A index at rest and the minimal GA index during PIRH) of more than 20%.
Using the six month postoperative result of a vascular reconstruction as the goldstandard, angiography appeared to be 80% sensitive, 50% specific and 58% accurate in assessing the hemodynamic significance of the aorto-iliac segment.
The positive predictive value (PPV) of angiography was 36% and the negative predictive value (NPV) 87%. When compared with FAP criteria as the goldstandard, angiography had a sensitivity of 50%, a specificity of 80% and an accuracy of 76%. The PPV was 30% and the NPV 90%. The low PPV values in both correlations indicate a tendency to overestimate the hemodynamic significance of lesions seen on a aorto-iliac angiogram.
The FAP criteria, when compared with the six month postoperative result of proximal reconstructions as the goldstandard, appeared to be 87% sensitive, 78% specific and 81% accurate in the prediction of significant aorto-iliac disease. The PPV was 70% and the NPV 91%. The conclusion was that the functional result of a vascular reconstruction

in the presence of multiple level disease, can be best predicted, when the decision to perform a distal or proximal reconstruction is based on a preoperative FAP test rather than on angiography. After this retrospective study, the FAP criteria were tested in a prospective study described in chapter IX.
Fourty-five symptomatic patients, with angiographic multiple-level disease, underwent a proximal or a distal reconstruction determined by the FAP criteria.
The six month postoperative result of the vascular reconstruction was used as the goldstandard for the correlation with the FAP criteria.
The conclusion was that the FAP criteria were 100% sensitive, 100% specific and 100% accurate in predicting the functional result of a vascular reconstruction in the presence of multiple-level disease. The PPV was 100% and the NPV was 100%. Eleven extremities were not included in these results for reasons outlined in the text.
Including these eleven cases in the calculations produces a 76% sensitivity, 100% specificity and 88% accuracy for the FAP criteria. The PPV remains 100% and the NPV is 80%.
The conclusion of this prospective study was that the FAP test is a simple and reliable method of predicting the functional result of a vascular reconstruction in the presence of multiple-level arterial obstructive disease seen at angiography.
The FAP criteria appear to be excellent indicators of the hemodynamic significance of lesions seen on a aorto-iliac angiogram, even in the presence of multiple-level disease.
The FAP test is invasive but this is a minor disadvantage as it can easily be combined with conventional angiography.

CONTENTS

Curriculum vitae auctoris

23-11-51	Born in Rotterdam.
1964-1970	Preacademic Study at the Marnix Gymnasium B, Rotterdam.
1970-1977	Medical study at the Free University, Amsterdam.
1978-1984	Training for General Surgeon at the St. Elisabeth Hospital, Tilburg. (Heads: Dr C.C.S.M. Wijffels, since 1983 Dr Th.J.M.V. van Vroonhoven).
1983-1984	Surgical Chef de Clinique in the St. Joseph and St. Maartens Hospital, Venlo.
1984-1985	Training for Cardio-Pulmonary Surgeon at the Dijkzigt University Hospital, Rotterdam. (Heads: Prof. Dr J. Nauta, Prof. Dr E. Bos).
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STELLINGEN

1. De laagste systolische enkel bloeddruk bij patienten met obstruerend arterieel vaatlijden van de onderste extremiteiten, tijdens post-ischemische en post-inspannings reactieve hyperemie, vertoont een goede correlatie. (Proefschrift).

2. Bij patienten met klachten suggestief voor obstruerend vaatlijden van de benen, is het verrichten van enkel bloeddruk onderzoek in rust essentieel; het routinematig verrichten van enkel bloeddruk onderzoek tijdens hyperemie is niet noodzakelijk. (Proefschrift).

3. Het meten van systolische bloeddruk aan de enkel, zowel in rust als tijdens reactieve hyperemie, is een ongeschikte methode om bij meer-etage afwijkingen, de plaats aan te duiden alwaar zich de hemodynamisch significante afwijkingen bevinden. (Proefschrift).

4. Intra-arteriele bloeddrukmeting in de arteria femoralis communis tijdens hyperemie, is, van de momenteel bekende diagnostische methoden, de meest geschikte om het aorto-iliacaal traject te beoordelen en derhalve het resultaat van een vasculaire reconstructie te voorspellen. (Proefschrift).

5. De angiografische beoordeling van het aorto-iliacaal traject correleert slecht met de beoordeling van dit traject op basis van intra-arteriele femoralis bloeddrukmetingen en eveneens slecht met de retrospectieve beoordeling van dit traject op basis van de post-operatieve resultaten van een vasculaire reconstructie. (Proefschrift).

6. De "receiver operator characteristic curve analysis" is een eenvoudige manier om de beste drempelwaarde van een testparameter te bepalen. (Pearce W.H., Yao J.S.T., Bergan J.J., Current Problems in Surgery 1983, 20: 461-538).

7. De behandeling van hemorrhoiden met een hemorrhoidectomie is zelden of nooit meer geindiceerd.

8. Korte, gelocaliseerde stenosen in de arteria iliaca lenen zich voor een behandeling door middel van transluminale angioplastiek; de resultaten van deze methode zijn zo goed, dat het niet meer verantwoord is bij deze patienten primair een operatieve vaatreconstructie uit te voeren.

9. De behandeling van choledocholithiasis, zeker bij de bejaarde patient, behoort niet langer primair tot het werkterrein van de chirurg, maar ook tot dat van de endoscopist.

10. Van de methode om met opzet huid en subcutis open te laten ten einde wondinfecties te voorkomen wordt, helaas, in het merendeel van de chirurgische klinieken niet of onvoldoende gebruik gemaakt.

11. Blauw is geen kleur, het is een toestand.

12. Ook voor leden van de chirurgische maatschap geldt: "In de Beschränkung zeigt sich der Meister".

- Stellingen behorende bij het proefschrift van P.F. Verhagen -